AUTOPSY STUDIES RELATING SMOKING, ATHEROSCLEROSIS, AND SUDDEN CHD DEATH

A number of researchers have investigated the cigarette smoking habits and the cardiovascular pathology of those individuals dying suddenly from CHD and of large populations of individuals with and without histories of overt CHD.

Spain and Bradess (*175*) recently analyzed the smoking habits of 189 individuals who died suddenly and unexpectedly, apparently from the first acute clinical episodes of CHD. The authors noted a close correlation of a history of cigarette smoking with this type of sudden death and also with shorter survival times following the acute episode. This association was strongest in those persons under 50 years of age.

The authors also observed that those surviving very short periods of time showed a notable lack of intracoronary artery thrombi at autopsy and that the frequency of thrombi present increased with increasing survival time. They suggested that thrombi found at autopsy may be the result rather than the cause of certain instances of myocardial infarction, particularly of lesions showing subendocardial necrosis. This finding is of significance in the study of the effect of smoking on myocardial metabolism and oxygen supply and demand rather than on thrombus or platelet plug formation.

While the autopsy study of Spain and Bradess (*175*) concerned sudden death among smokers, other autopsy studies from various countries have been directed towards the relationship of cigarette smoking to the presence of atherosclerotic disease in the aorta and coronary arteries. These are concerned with the long-term effects which smoking has on the cardiovascular system and are summarized in table 19. The studies of Auerbach, et al. (*12*), Avtandilov, et al. (*13*), Sackett, et al. (*165*), and Strong, et al. (*182*) found that aortic and coronary atherosclerosis were more common and more severe among smokers than among nonsmokers. Auerbach, et al. (*12*) noted that this relationship persisted when the cases were matched for both age and cause of death or when the following cases were excluded: men with a history of diabetes; men who had died of any type of heart disease; and men whose hearts weighed 400 grams or more. Sackett, et al. (*165*) found that the severity of aortic atherosclerosis, as measured both by intensity and duration, increased with increasing use of cigarettes and that this dose-relationship persisted when the patients were matched for the consumption of alcohol. On the other hand, Viel, et al. (*200*) concluded from their study of accidental deaths in Chile that "no relationship between atherosclerotic lesions and the use of tobacco was discernible." Examination of the data (provided in graph form only) indicates that heavy smokers showed consistently higher percentages of diseased areas than nonsmokers, but apparently these differences were not statistically significant when subjected to an analysis of variance.

Thus, in addition to the acute effects which smoking exerts on cardiovascular physiology, cigarette smoking is associated with a significant increase in atherosclerosis.

(175) SPAIN, D. M., BRADESS, V. A. Sudden death from coronary heart disease. Survival time, frequency of thrombi, and cigarette smoking. Chest 58(2): 107–110, August 1970.

(12) AUERBACH, O., HAMMOND, E. C., GARFINKEL, L. Smoking in relation to atherosclerosis of the coronary arteries. New England Journal of Medicine 273(15): 775–779, October 7, 1965.

(13) AVTANDILOV, G. G., KOLENOVA, V. I., PONOMARENKO, O. V. Kureniye tabaka i stepen' ateroskleroticheskogo porazheniya koronarnykh arteriy serdtsa i aorty. (Tobacco smoking and the degree of atherosclerotic lesions of coronary arteries of the heart and aorta.) Kardiologiya 5(1): 30–34, January-February 1965.

(165) SACKETT, D. L., GIBSON, R. W., EROSS, I. D. J., PICKREN, J. W. Relation between aortic atherosclerosis and the use of cigarette and alcohol. An autopsy study. New England Journal of Medicine 270(26): [illegible]

(182) STRONG, J. P., RICHARDS, M. L., MCGILL, H. C., JR., EGGEN, D. A., MCMURRAY, M. T. On the association of cigarette smoking with coronary and aortic atherosclerosis. Journal of Atherosclerosis Research 10(3): 303–317, November–December 1969.

(200) VIEL, B., DONOSO, S., SALCEDO, D. Coronary atherosclerosis in person dying violently. Archives of Internal Medicine 122(2): 97–103, August 1963.

100505746

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

Interpretation of Sudden Deaths. The interpretation of (175) Spain and Bradess is different from the original one by the authors. The last paragraph in the Discussion should be noted.

Discussion

The current findings of an increase in frequency of coronary thrombi with an increase in duration of survival from the onset of the clinical manifestations of the coronary heart attack are almost identical with those of the study reported in 1961.[8] Regardless of the interpretation of these findings, the fact that the results are identical in studies performed almost ten years apart would support the validity of these observations. The concept that some mechanism other than that the formation of a new thrombus triggers the onset of many coronary heart attacks is again restated and that it is during the early phases of this "attack," in progress, that arrhythmias or metabolic deficiencies in the myocardium disturb the hemodynamics of an already embarrassed coronary circulation to favor the formation of a thrombus in a vessel previously compromised by atherosclerosis. This additional obstruction to the circulation enhances the ischemia sufficiently to now produce a transmural infarct which otherwise might not have developed. With increasing time of survival and with the persistence of a myocardial metabolic disturbance and arrhythmia, there is a greater opportunity for such thrombi to develop. In this connection it is pertinent to note that in an experimental study on calves the induction of prolonged ventricular fibrillation was accompanied by massive subendocardial damage.[9] No thrombi were present and the severity of the myocardial lesions increased with the duration of the experiment.

With presently available autopsy techniques it is difficult if not impossible to obtain additional information for further support for the concept of the secondary origin of many coronary thrombi. Autopsies unfortunately provide only one still picture of a process which during life is rapidly evolving, changing and dynamic. The cause often cannot be distinguished from effect. If there is to be confirmation or rejection of this concept it may have to await the time when there will be enough cases from the mobile coronary care unit experiences, who have been treated within the first 30 minutes of the onset of the attack and who have survived for a sufficient length of time. It will then be possible to determine whether these survivors reveal greater or lesser numbers of transmural infarcts than anticipated from experience previously. A significant decrease in this type of infarct which is usually associated with coronary thrombi would contribute important support for the concept of a secondary development of the thrombus after the onset of the attack. This would provide early encouragement for intervention in an attempt to interrupt those processes favoring the formation of thrombi.

The findings also support the view that cigarette smoking exerts some if not its major harmful effects on the acute clinical event rather than on the chronic atherogenic process. The fact that fewer coronary thrombi were present in the more than one pack per day cigarette smokers can be explained by the observation that these are the very cases with the shortest survival and the number of thrombi are noted to increase with longer survival.

The cases in this study were drawn from an overall group of 500 consecutive Medical Examiner autopsies. The smoking history questionnaires had been sent to the next of kin in all of these cases. There were 60 percent respondents. However, the age distribution, sex ratio and causes of death were similar in the autopsies with respondents and nonrespondents. The frequency of coronary thrombi and duration of survival from onset of "attack" were also similar in the respondent and nonrespondent groups. The smoking patterns of the Medical Examiner population as whole in the respondent group showed a ratio of 1 nonsmoker to 1.3 more than 20 cigarettes per day smokers. The ratio in the population from which the Brookdale Hospital autopsies were drawn was 1 nonsmoker to every 1.4 more than 20 cigarettes per day smokers. However, it should be noted that no smoking comparisons were made in the study with the group that survived more than eight hours. Unfortunately, the nature of the problem precludes sufficient numbers of more than eight hour survivors from a Medical Examiner case study as they are admitted to the hospital and therefore upon death do not become Medical Examiner cases. At any rate, the selected population upon which this study was of necessity based, precludes the unconditional generalization of these findings to the population at large.

1005050747

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

TABLE 19.—*Autopsy studies of atherosclerosis*

(Figures in parentheses are number of individuals in that smoking category)[1]

[SM = smokers NS = nonsmokers]

Author, year, country, reference	Autopsy population	Data collection	Cigarettes per day	Severity of aortic sclerosis: Above average	Average	Below average	Conclusions	Comments
Wilens and Plair, 1962, U.S.A. (*214*).	959 consecutive male autopsies at New York City VA hospitals.	Routine clinical records of previous and present admissions.	NS ..... 9.9(161)		40.2	29.8	The authors conclude that in 60 percent of cases, the degree of sclerosis at autopsy was commensurate with age of patient, regardless of smoking habits. In the remaining 40 percent there is evidence that cigarette smoking may be associated with an above-average degree of aortic sclerosis.	Smoking data unavailable for 120 cases. Each aorta specimen given an "atherosclerotic age" by comparison with a standard. If "atherosclerotic age" was found to be 10 years more than real age, the aorta was said to show above-average sclerosis. †p<0.001 comparing 9.9 with 25.1 and 29.8 with 13.6.
			<20 ..... 19.1(152)		63.2	17.6		
			20–39 ..... 26.4(268)		62.5	11.1		
			>39 .....†28.1(199)		61.3	†13.6		

(*214*) WILENS, S. L., PLAIR, C. M. Cigarette smoking and arteriosclerosis. Science 138: 975–977, November 30, 1962.

Author, year, country, reference	Autopsy population	Data collection	Degree of coronary artery atherosclerosis (overall age-adjusted results): No atherosclerosis	Slight	Moderate	Advanced	Conclusions	Comments
Auerbach, et al., 1963, U.S.A. (*18*).	1,372 autopsies of male patients in Orange, New Jersey, VA — hospital for whom smoking habit data were available and who did not have overt CHD at death.	Interview with next of kin.	NS 5.6 (69)	57.8	21.8	15.3	The authors conclude that the percentage of men with an advanced degree of coronary atherosclerosis was higher among cigarette smokers than among nonsmokers and that the percentage increased with amount of cigarette smoking. This relationship persisted even when cases were matched for age and cause of death.	
			Current cigarette					
			<20 .....2.6(129)	30.9	37.8	29.2		
			20–39 ....0.8(299)	19.7	42.1	37.4		
			>40 .....0.6(144)	16.1	38.4	45.8		

[1] Unless otherwise specified, disparities between the total number of individuals and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

(Figures in parentheses are number of individuals in that smoking category)[1]

[SM = smokers NS = nonsmokers]

Author, year, country, reference	Autopsy population	Data collection	Cigarettes per day	Comparative size of mean area of atherosclerotic lesions in inner coat of coronary arteries. Right coronary artery: SM	NS	Left coronary artery: SM	NS	Conclusions	Comments
Avtandilov, 1965, Russia (*13*).	259 male and 141 female autopsies.	Not specified, but there were: 180 SM and 220 NS.	30–39 ..†15.5(30)	1.3(32)	†3.3	3.2	The author concludes that the worst changes were found in the left and right coronary arteries with less severe changes in circumflex artery and aorta.	Causes of death 96-atherosclerotic, 102-accidental, 202-various diseases. †T-test for significance of difference between means is significant at p<0.05 level.
			40–49 ..†23.6(34)	11.5(27)	†15.8	4.4		
			50–59 ..†26.2(39)	14.9(33)	†27.9	9.9		
			60–69 ..†31.9(52)	23.8(35)	†26.5	22.5		
			70–79 .. 41.9(18)	11.7(36)	26.1	15.8		
Sackett, et al., 1968, U.S.A. (*165*).	893 total, including 433 male and 450 female (white) patients autopsied at Roswell Park Memorial Hospital. Represents all deaths 1956–1964 exclusive of 51 male pipe and cigar smokers and 65 incomplete files.	Patient interview on admission.	The results concerning aortic atherosclerosis are given in form of figure presentation of ridit-analysis.				The authors conclude that among males, "... a large increase in the severity of aortic atherosclerosis occurred in the groups using either cigarettes only or both cigarettes and alcohol as compared with the group using neither cigarettes nor alcohol ... there was only a small and statistically insignificant difference between the group using cigarettes alone and the group using both cigarettes and alcohol, ..." The severity of aortic atherosclerosis increased with increasing use of cigarettes, when measured both by intensity and by duration of smoking.	

[1] Unless otherwise specified, disparities between the total number of individuals and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

10050748

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

Coronary Blood Flow

Studies in animals and humans (tables A20, A21) have noted alterations in coronary blood flow (CBF) following the inhalation of cigarette smoke or the administration of nicotine. Generally, exposure of the normal subject to these agents results in an increase in flow. Kien and Sherrod (*112*), Leb, et al. (*126*), Ross and Blesa (*160*), Travell, et al. (*189*), and West et al. (*208*), working with normal animals, and Bargeron, et al. (*17*), working with normal humans, have demonstrated this response. As with the other cardiac responses to the administration of nicotine, it has been found that the augmentation in CBF is most probably due to the release of catecholamines. Using instantaneous coronary arterial flow measurement in dogs, Ross and Blesa (*160*) were able to reproduce the effects of intracoronary nicotine with the administration of epinephrine and were able to block the response to nicotine by pretreatment with pentolinium.

The direct action of catecholamines on the coronary arteries may not, however, be solely responsible for the increase in CBF seen with cigarette smoking and intravenous nicotine administration. It appears that the catecholamine-induced increase in myocardial work and therefore in myocardial oxygen requirement is a prerequisite for the increase in CBF. Kien and Sherrod (*112*), using tracheostomized dogs, found that without blood pressure and cardiac output changes CBF did not increase following either the inhalation of cigarette smoke or the administration of nicotine intravenously, although CBF did increase following such changes. Recent work by Leb, et al. (*126*) has utilized Rb^{86} as a radioactive marker in order to distinguish capillary flow from overall total CBF. The authors consider that this capillary flow represents that portion of CBF which is effectively involved in nutrient and oxygen exchange. The researchers observed that the increase in effective coronary flow was almost proportional to the nicotine-induced increase in myocardial oxygen consumption. However, the increase in total coronary flow which may be due to increased myocardial shunting was far in excess. Thus, the increased work evoked by the effect of nicotine on the myocardium may induce local hormonal release in the myocardium and coronary vessels leading to coronary vasodilatation and increased CBF.

This homeostatic response to increased work appears to be fully effective only in the subjects with normal coronary arteries. Bellet, et al. (*22*), working with normal dogs and dogs that had undergone either coronary artery ligation or artificially-induced coronary artery narrowing, noted that the increase in CBF following the intravenous administration of nicotine was significantly less among the animals with coronary insufficiency. Work with humans discussed above has revealed a similar increase in CBF with smoking in normals. Regan, et al. (*154*) studied seven men with EKG-proven myocardial infarction and observed that cigarette smoke evoked slight increases in myocardial oxygen consumption in only three patients and caused no overall rise in CBF. A number of other investigators have noted that patients with overt CHD do not respond to the stimulus of cigarette smoke as readily as do normals (*67, 149, 164*).

Thus, patients with compromised coronary circulation may not be capable of increasing their coronary flow in the face of the increased demands of a myocardium stimulated by nicotine or cigarette smoke. In the normal state, the heart responds to increased oxygen demands by increasing coronary flow because even at rest oxygen extraction is almost at a maximal level. Any further increase in extraction may produce coronary sinus pO_2 values incompatible with proper tissue oxygenation.

(126) Leb, G., Dernti, F., Robin, E., Bing, R. J. The effect of nicotine on effective and total coronary blood flow in the anesthetized closed-chest dog. Journal of Pharmacology and Experimental Therapeutics 173 (1): 138–141, May 1970.

(189) Travell, J., Rinzler, S. H., Karp, D. Cardiac effects of nicotine in the rabbit with experimental coronary atherosclerosis. Annals of the New York Academy of Sciences 90(1): 290–301, September 27, 1960.

(17) Bargeron, L. M., Jr., Ehmke, D., Conlubol, F., Castellanos, A., Siegel, A., Bing, R. J. Effect of cigarette smoking on coronary blood flow and myocardial metabolism. Circulation 15: 251–257, February 1957.

(22) Bellet, S., West, J. W., Muller, O. F., Manzoli, U. C. Effect of nicotine on the coronary blood flow and related circulatory parameters. Correlative study in normal dogs and dogs with coronary insufficiency. Circulation Research 10(1): 27–34, January 1962.

(154) Regan, T. J., Hellems, H. K., Bing, R. J. Effect of cigarette smoking on coronary circulation and cardiac work in patients with arteriosclerotic coronary disease. Annals of the New York Academy of Sciences 90(1): 186–189, September 27, 1960.

(67) Frankl, W. S., Winters, W. L., Soloff, L. A. The effects of smoking on the cardiac output at rest and during exercise in patients with healed myocardial infarction. Circulation 31(1): 42–44, January 1965.

(149) Pentecost, B., Shillingford, J. The acute effects of smoking on myocardial performance in patients with coronary arterial disease. British Heart Journal 26: 422–429, 1964.

(164) Russek, H. I., Zohman, B. L., Dorset, V. J. Effects of tobacco and whiskey on the cardiovascular system. Journal of the American Medical Association 157(7): 563–568, February 12, 1955.

1005050749

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

Nicotine on Coronary Blood Flow. In this section on Coronary Blood Flow, the effects of cigarette smoking or nicotine injection on canine or human subjects are described together, ignoring the differences between them. After describing the conclusion of (126) Leb et al., a concept is described which states that nicotine increases cardiac work directly, which may in turn induce the release of catecholamines. Leb et al. did not propose such a scheme and nobody else has until the appearance of the 1971 document.

Our results show that myocardial oxygen consumption increases after nicotine administration; this occurs as left ventricular work rises. It was shown previously that nicotine augments the contractile state of the myocardium (Puri *et al.*, 1968). The increase in myocardial oxygen consumption is expected, since the drug augments the contractile state of the heart and cardiac work (Sonnenblick *et al.*, 1968). As a result, the increase in myocardial oxygen demands are met by an increase in the effective coronary flow. Figure 1 shows that capillary flow increases almost proportionally to myocardial oxygen consumption, whereas the increase in total coronary flow is far in excess of myocardial oxygen consumption; this suggests that effective capillary flow measured by this method is more closely related to myocardial oxygen consumption than is total coronary flow.

The results reported here do not permit any conclusions on the exact location of the action of nicotine. It is possible that nicotine, like norepinephrine, decreases coronary vascular resistance (Winbury *et al.*, 1965); this could increase effective coronary flow up to a limit, above which there cannot take place any further rise in effective capillary flow as total coronary flow increases. Only direct observations on the microcirculation similar to those carried out by Wayland *et al.* (1967) will permit more definitive conclusions on this point.

Conclusions. Intravenous administration of nicotine (100 μg/kg in one minute) in the healthy, closed-chest, anesthetized dog caused increases in left ventricular work, in myocardial oxygen consumption and in both effective (nutritional) and total coronary flow.

The increase in effective capillary flow to the myocardium after nicotine administration was sufficient to meet myocardial oxygen demands. Effective capillary flow appeared to be primarily regulated by myocardial oxygen consumption. The proportional increase in myocardial oxygen consumption and effective capillary flow indicates that the effective capillary flow to the myocardium is closely related to myocardial oxygen supply.

1005050250

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

Carbon monoxide (CO) is a colorless and odorless gas, low levels of which have significant effects on human and animal physiology which are just now beginning to be understood. According to Wynder and Hoffmann (315), it is present in cigarette smoke in concentrations of approximately 2.9 to 5.1 percent. The concentration of CO in smoke is subject to many factors, among them the type of tobacco and the porosity of cigarette paper. The concentration of CO in smoke has been found to increase significantly toward the last puffs of the cigarette.

According to Chevalier, et al. (71), a concentration of approximately 4 percent CO in cigarette smoke will produce alveolar levels of around 0.04 percent which, equilibrated with hemoglobin, result in carboxyhemoglobin (COHb) concentrations of from 3 to 10 percent. A number of investigators have compared COHb levels in smokers and nonsmokers. Goldsmith and Landaw (79) reported the analysis of expired air samples obtained from 3,311 longshoremen. Using a regression analysis, they calculated the concentration of COHb and found that nonsmokers showed levels of 1.2 percent while those smoking over 2 packs per day had levels of 6.8 percent and that smokers of lesser amounts had intermediate levels. Occupational exposure accounted for the mean nonsmokers' level being over 1.0 percent, an unusual finding in comparison with other studies. Kjeldsen (178) interviewed and obtained blood samples from 931 CHD-free smokers and nonsmokers. The mean COHb level for 196 nonsmokers was 0.4 percent while all inhaling smokers had a mean level of 7.3 percent. All 416 cigarette smokers, regardless of inhalation or amount smoked, showed a mean level of 4.0 percent.

Carbon monoxide has many varied and significant effects on human physiology. An overall review of these effects may be found in a discussion by Lilienthal (127) or more recently in an extensive review by the United States Public Health Service National Air Pollution Control Administration (194). Apart from its effects on respiratory and circulatory function, CO has been found to affect certain central nervous system functions adversely. These effects are probably due to interference by CO with the proper oxygenation and oxidative metabolism of the tissue in question.

CO interferes with oxygen transport in a variety of ways. First, the affinity of hemoglobin for CO is approximately 200 times greater than its affinity for oxygen, and thus CO can easily displace oxygen from hemoglobin. Second, CO shifts the oxyhemoglobin dissociation curve. By increasing the avidity with which oxygen is bound by hemoglobin, CO interferes with O_2 release at the tissue level. This is of greatest importance at the tissue level where the oxygen content of the capillary blood has been reduced to approximately 40 percent saturation. Here the shift can substantially decrease the oxygen tension supplying the tissues.

Third, and of more recent note, is the possible interference by CO with the homeostatic mechanism by which 2, 3-diphosphoglycerate (2, 3-DPG) controls the affinity of hemoglobin for oxygen. Bunn and Jandl (34) have recently reviewed the various experiments concerning this glycolytic intermediate. The question of whether the low levels of CO present in the blood of smokers can affect this homeostasis is presently under investigation (29, 113), and firm conclusions cannot be drawn at this time.

Apart from its effect on hemoglobin affinity, CO appears to induce arterial hypoxemia, and this may act as an additional cause of tissue hypoxia. Ayres, et al. (15, 16) observed unexpectedly that exposure of individuals to CO sufficient to raise their levels of COHb to between 5 and 10 percent was associated with a significant fall in arterial pO_2. Greater fall in venous pO_2 was noted, but this was considered secondary to increased tissue extraction. In a recent article, Brody and Coburn (30) suggested that this COHb-induced arterial hypoxemia was due to the interaction of a number of factors. These authors noted that in the presence of veno-arterial shunts or of an imbalance in the ventilation-perfusion ratio, the shift in the oxyhemoglobin dissociation curve increased the alveolar-arterial O_2 gradient and resulted in arterial hypoxemia. The presence of shunts as small as 2 percent of cardiac output as well as of approximately 10 percent COHb was found to cause an increase in the gradient. Such ventilation-perfusion (V/Q) abnormalities have recently been noted even in asymptomatic smokers (see Chapter on Chronic Obstructive Bronchopulmonary Disease). The increased levels of COHb found in the blood of smokers may interact with these V/Q abnormalities to further decrease available oxygen.

(315) WYNDER, E. L., HOFFMANN, D. Tobacco and Tobacco Smoke. Studies in Experimental Carcinogenesis. New York, Academic Press, 1967. 730 pp.

(71) CHEVALIER, R. D., KRUMHOLZ, R. A., ROSS, J. C. Reaction of nonsmokers to carbon monoxide inhalation. Cardiopulmonary responses at rest and during exercise. Journal of the American Medical Association 198(10): 1061-1064, December 5, 1966.

(79) GOLDSMITH, J. R., LANDAW, S. A. Carbon monoxide and human health. Science 162(3860): 1352-1359, December 20, 1968.

(178) KJELDSEN, K. Smoking and Atherosclerosis. Investigations on the significance of the carbon monoxide content in tobacco smoke in atherogenesis. Copenhagen, Munksgaard, 1969. 145 pp.

(127) LILIENTHAL, J. L., JR. Carbon monoxide. Pharmacological Review 2: 324-354, 1950.

(194) U.S. PUBLIC HEALTH SERVICE. NATIONAL AIR POLLUTION CONTROL ADMINISTRATION. Air Quality Criteria for Carbon Monoxide. Washington, U.S. Department of Health, Education and Welfare, National Air Pollution Control Administration Publication No. AP-62, March 1970. 153 pp.

(34) BUNN, H. F., JANDL, J. H. Control of hemoglobin function within the red cell. New England Journal of Medicine 282(25): 1414-1421, June 18, 1970.

(29) BREWER, G. J., EATON, J. W., WEIL, J. V., GROVER, R. F. Studies of red cell glycolysis and interactions with carbon monoxide, smoking, and altitude. Advances in Experimental Medicine and Biology 6: 95-114, 1970.

(113) OSKI, F. A., GOTTLIEB, A. J., MILLER, W. W., DELIVORIA-PAPADOPOULOS, M. The effects of deoxygenation of adult and fetal hemoglobin on the synthesis of red cell 2,3-diphosphoglycerate and its in vivo consequences. Journal of Clinical Investigation 49(2): 400-407, February 1970.

(15) AYRES, S. M., GIANNELLI, S., JR., ARMSTRONG, R. G. Carboxyhemoglobin: Hemodynamic and respiratory responses to small concentrations. Science 149: 193-194, July 9, 1965.

(16) AYRES, S. M., MUELLER, H. S., GREGORY, J. J., GIANNELLI, S., JR., PENNY, J. L. Systemic and myocardial hemodynamic responses to relatively small concentrations of carboxyhemoglobin (COHB). Archives of Environmental Health 18(4): 699-709, April 1969.

(30) BRODY, J. S., COBURN, R. F. Carbon monoxide-induced arterial hypoxemia. Science 164(3885): 1297-1298, June 13, 1969.

1005051

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

In normal individuals, coronary flow can increase to meet the increased oxygen demands of a stressed myocardium (as that under nicotine stimulation), while in individuals with severe CHD coronary flow cannot respond as readily. In such cases, myocardial oxygen extraction must be increased above the almost maximal extraction found at rest. Any interference with arterial oxygen levels or hemoglobin affinity could very well decrease available oxygen supplies below the level required for proper tissue function. That this occurs is suggested by the experiments discussed below.

Chevalier, et al. (121) exposed 10 young nonsmokers to CO concentrations sufficient to induce COHb levels of approximately 4 percent. Taking measurements from blood specimens obtained at cardiac catheterization under resting and exercise conditions, the authors noted that the ratio of oxygen debt to oxygen uptake increased significantly under conditions of increased COHb. According to the investigators this implied that the same work was being done at a greater metabolic cost. These same authors (121, 122) had previously noted similar findings among smokers and observed that cessation of smoking was associated with a significant improvement in oxygen debt accumulation.

More recent work by Ayres, et al. (15) has focused on the difference in response to CO exposure between 7 normals and 4 patients suffering from CHD (proven arteriographically). The induction of a COHb concentration of approximately 9 percent in the normals was followed by an increase in coronary blood flow, a decrease in hemoglobin-oxygen percent extraction and no change in myocardial oxygen consumption, coronary sinus oxygen tension, and lactate and pyruvate extraction ratios. The induction of similar COHb levels in the CHD patients was followed by no change in coronary blood flow, a decrease in the hemoglobin-oxygen extraction ratio, and no change in myocardial oxygen consumption. However, these patients did manifest a decrease in coronary sinus pO_2 as well as a decrease in lactate and pyruvate extraction. The latter measures indicate that the myocardium was functioning under hypoxic conditions. Because the coronary flow could not increase and because the myocardium could not extract O_2 from arterial O_2 which was under the influence of CO, coronary sinus oxygen tension decreased to a point which could inactivate certain oxidative enzyme processes. Thus, the myocardial function of persons with CHD may be unable to compensate for the stresses induced by smoking.

Although COHb levels resulting from the CO present in the atmosphere during periods of high air pollution are much lower than those due to the inhalation of cigarette smoke, these concentrations of COHb might contribute to the manifestations of CHD. Cohen, et al. (44) studied the case fatality rates for patients admitted to 35 Los Angeles area hospitals with myocardial infarction in relation to atmospheric CO pollution. The authors observed an increased MI case fatality rate in areas of increased pollution, and seen only during periods of relatively increased CO pollution.

Still an area of interest which has been discussed in previous reports concerns the presence of hydrogen cyanide in tobacco smoke. According to Wynder and Hoffmann (215), the amount present ranges from 11 to 32 micrograms HCN per puff. It is known that a significant amount of this material is detoxified to thiocyanate and excreted as such in the urine or saliva. However, cyanide is a potent inhibitor of oxidative metabolism. Such inhibition of myocardial oxidative metabolism may be of importance when combined with the other factors mentioned above which tend to decrease the oxygen supply available and increase the need for oxygen on the part of the myocardium.

(121) KRUMHOLZ, R. A., CHEVALIER, R. B., ROSS, J. C. Cardiopulmonary function in young smokers. A comparison of pulmonary function measurements and some cardiopulmonary responses to exercise between a group of young smokers and a comparable group of nonsmokers. Annals of Internal Medicine 60(4): 603–610, April 1964.

(122) KRUMHOLZ, R. A., CHEVALIER, R. B., ROSS, J. C. Changes in cardiopulmonary functions related to abstinence from smoking. Studies in young cigarette smokers at rest and exercise at 3 and 6 weeks of abstinence. Annals of Internal Medicine 62(2): 197–207, February 1965.

(44) COHEN, S. I., DEANE, M., GOLDSMITH, J. R. Carbon monoxide and survival from myocardial infarction. Archives of Environmental Health 19(10): 510–517, October 1969.

10050752

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

Effects of Smoking on the Formation of Atherosclerotic Lesions

A number of autopsy studies have demonstrated a significant association between cigarette smoking and the presence of aortic and coronary artery atherosclerosis, even in men without a history of clinical CHD. The possible pathophysiologic mechanisms for the atherogenic influence of cigarette smoking are discussed in this section.

A number of investigators have studied the effect of nicotine administration, either subcutaneously or intravenously, upon atherosclerotic changes in the aorta and coronary arteries of animals (table A22). When administered alone, nicotine induces certain necrotic changes in the arterial wall. However, in combination with the administration of increased amounts of cholesterol in the diet, nicotine aggravates either subendothelial fibrosis (*75*) or definite atheromatous lesions (*36, 75, 80, 130, 178*). Studies by Choi (*42*) and by Wenzel, et al. (*207*) did not demonstrate this synergism between cholesterol and nicotine.

The other major cigarette smoke component under discussion in this chapter, carbon monoxide, has also been recently implicated in atherogenesis. Table 24 presents the studies which have related exposure to CO in combination with increased dietary cholesterol to both macroscopic and microscopic aortic and coronary atheromatosis. Astrup, et al. (*10*) exposed cholesterol-fed rabbits to CO continually over a period of up to 10 weeks. The experimental group showed increased aortic atheromatosis over that shown by the control group, also cholesterol-fed. Kjeldsen, et al. (*114*) observed that exposure of rabbits to increased oxygen concentrations significantly reduced the amount of cholesterol-induced atheromatosis in rabbits. Most recently, Webster, et al. (*204*) have extended this research to primates. These investigators found that cholesterol-fed squirrel monkeys developed significantly more coronary artery atherosclerosis when exposed intermittently to CO over a 7-month period than when exposed only to room air.

Recent discussion has centered on the mechanisms whereby CO can induce these changes (*9, 212*). Astrup (*9*), referring to previous experiments in humans which had shown increased vascular permeability for albumin upon chronic exposure to CO (*11*), considers it likely that this increase in permeability allows for increased filtration of lipoproteins into arterial walls. This, he considers, is a primary cause of intimal and medial lipid accumulation and, therefore, of atherosclerosis.

Another point of view has been stressed by Whereat (*212*), who considers the filtration theory to be an inadequate hypothesis for mural lipid accumulation. The author notes that when the oxidation of the pyridine nucleotide, nicotinamideadenine dinucleotide (NAD), is impaired, the reduced form of this nucleotide (NADH) provides an essential factor for fatty acid synthesis. Fatty acid synthesis in the aorta and heart is carried out by mitochondrial enzymes whose hydrogen donor is NADH. Substances which slow or impair the reoxidation of this compound tend to increase mitochondrial fatty acid synthesis (and decrease fatty acid utilization) in the arterial wall. Carbon monoxide prevents this oxidation process both directly and indirectly. Indirectly, it decreases the oxygen available for diffusion into the tissue. Directly, carbon monoxide can stall the process of NADH oxidation by combining with cytochrome oxidase. Further research is required into this problem, particularly in view of the fact that cyanide is also a respiratory chain inhibitor and thus may also adversely affect arterial wall fat metabolism.

(75) Grosgogeat, Y., Anguera, G., Lellouch, J., Jacotot, B., Beaumont, J.-L., Patois, E., Manier, E. L'intoxication chronique par la nicotine chez le lapin nourri au cholesterol. Effets sur la paroi aortique et sur la lipidemie. (Chronic nicotine poisoning in the rabbit on a cholesterol diet. Effects on the wall of the aorta and on lipidemia.) Journal of Atherosclerosis Research 5(2): 291–301, 1965.

(36) Czochra-Lysanowicz, Z., Gorski, M., Kedra, M. Wplyw nikotyny i kofeiny na rozwoj miazdzycy u krolikow. (The effect of nicotine and caffeine on the development of arteriosclerosis in rabbits.) Annales Universitatis Mariae Curie-Sklodowska; Section D: Medicina 14(20): 181–206, 1959.

(80) Kass, G. M., Landenholm, W., Hemmens, A. Production of calcific athero-arteriosclerosis and thromboarteritis with nicotine, vitamin D, and dietary cholesterol. American Journal of Pathology 49(4): 739–771, October 1966.

(130) Maslova, K. K. The influence of nicotine on experimental atherosclerosis. Bulletin of Experimental Biology and Medicine 41: 20–23, 1956.

(178) Stefanovich, V., Gore, I., Kajiyama, G., Iwanaga, Y. The effect of nicotine on dietary atherogenesis in rabbits. Experimental and Molecular Pathology 11(1): 71–81, August 1969.

(42) Choi, Y. Y. Effect of nicotine upon cholesterol-induced atherosclerosis in rabbits. New Medical Journal 10(7): 685–692, 1967.

(207) Wenzel, D. G., Turner, J. A., Kissil, D. Effect of nicotine on cholesterol-induced atherosclerosis in the rabbit. Circulation Research 7: 256–261, March 1959.

(10) Astrup, P., Kjeldsen, K., Wanstrup, J. Enhancing influence of carbon monoxide on the development of atheromatosis in cholesterol-fed rabbits. Journal of Atherosclerosis Research 7: 343–354, 1967.

(114) Kjeldsen, K., Astrup, P., Wanstrup, J. Reversal of rabbit atheromatosis by hyperoxia. Journal of Atherosclerosis Research 10(2): 173–178, September-October 1969.

(204) Webster, W. S., Clarkson, T. B., Lofland, H. B. Carbon monoxide-aggravated atherosclerosis in the squirrel monkey. Experimental and Molecular Pathology 13(1): 36–50, 1970.

(9) Astrup, P. Effects of hypoxia and of carbon monoxide exposures on experimental atherosclerosis. Annals of Internal Medicine 71(2): 426–427, August 1969.

(212) Whereat, A. F. Is atherosclerosis a disorder of intramitochondrial respiration? Annals of Internal Medicine 73(1): 125–127, July 1970.

(11) Astrup, P., Pauli, H. G. (Editors). A Comparison of Prolonged Exposure to Carbon Monoxide and Hypoxia in Man. Reports of a Joint Danish-Swiss Study. Scandinavian Journal of Clinical and Laboratory Investigation 22 (Supplement 103): 1968. 71 pp.

1005050753

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

Atherosclerotic Lesions in the Rabbit. The conflicting results reported by (207) Wenzel et al. and (178) Stefanovich et al. need some explanation because the emphasis differs between the two. Wenzel, in addition to gross examination of the aorta also stressed the animal with ergonovine to induce abnormalities in the ECG. Stefanovich analyzed cholesterol in the aorta and found that the level was lower in the nicotine treated rabbit. There are numerous problems in using cholesterol fed rabbits, yet this is the animal which serves as the basis for the claim that smoking causes atherosclerosis. Note the differences in conclusions between Wenzel (top) and Stefanovich (bottom).

SUMMARY

Rabbits (New Zealand, albino, females) on a cholesterol (1%) diet and injected with nicotine (2.78 mg/kg 5 days a week for 6 weeks) demonstrated wider areas of involvement of the intima (19.4% vs. 5.7%) in the aorta than rabbits on a cholesterol diet alone. In both *stock*-fed and cholesterol-fed animals, nicotine produced an increase in aortic triglycerides and a decrease in the free cholesterol content. An increase in phospholipids, particularly in lecithin and cephalin, was observed in the cholesterol-fed rabbits treated with nicotine. Aortic acid mucopolysaccharide composition did not exhibit any significant changes following nicotine treatment.

In experiments *in vitro*, it was shown that heparin and nicotine form a relatively stable complex, in a molar ratio of about 1:20; nicotine also inhibits the hydrolysis of ^{14}C-labeled triolein in a homogenate from rabbit aortic tissue. It is suggested that some of the biological effects of nicotine may be the result of a complex formation between nicotine and heparin *in vivo*.

SUMMARY

Groups of female albino rabbits [illegible] administered cholesterol, nicotine, and cholesterol for a 24 week period. [illegible] addition of nicotine to the cholesterol regimen did not significantly affect body weight, cholesterol or lipid phosphorus or gross atherosclerosis under the conditions of this test. The nicotine-cholesterol group demonstrated greater mortality, as well as greater electrocardiographic and pathologic evidence of cardiac involvement and peripheral vascular changes, than did the cholesterol or nicotine groups. It is suggested that the combination of nicotine and cholesterol produces a cardiovascular interaction.

1005050254

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

The Effect of Smoking on Thrombosis

In the study of CHD, a number of investigators have turned their attention to thrombosis because myocardial infarction and sudden coronary death frequently result from thrombotic events. A thrombus may be of either gross or microscopic dimensions, and a minute thrombus at a strategic site may precipitate a fatal arrhythmia. However, thrombotic and prethrombotic states are difficult to detect except when gross, and the emphasis has been primarily on factors which can be studied conveniently. Coagulation is now thought to have a secondary role in the consolidation of an arterial thrombus and little if any in initiating the process. The prime mechanism in thrombogenesis appears to be the reaction of the platelet. Several papers have been written about platelet reactivity *in vitro* but few about the effect of smoking on platelet behavior *in vivo*. The assay of fibrinolysis, which may also be important, has received scanty treatment. The relevant studies are listed in table A27. Many of these are discussed in the 1968 supplement (*192*) and by Murphy (*140*). Corroborative data are still inconclusive as to whether smoking shortens platelet survival.

(140) Murphy, E. A. Thrombozyten, Thrombose und Gerinnung. (Thrombocytes, thrombosis and clotting.) IN: Schievelbein, H. (Editor). Nikotin: Pharmakologie und Toxikologie des Tabakrauches. Stuttgart (West Germany), Georg Thieme Verlag, 1968. pp. 178–192.

The Effect of Smoking on Serum Lipid Levels

In the discussion concerning the epidemiological aspects of CHD, it was noted that increased serum cholesterol was a significant risk factor for the development of overt CHD. Serum triglycerides have also been related to CHD incidence. Of concern also is the immediate effect which cigarette smoking has upon blood lipid levels.

The studies concerning this immediate effect are presented in tables A 25 and A 25a. The table is divided into a section concerning studies on humans (table A 25) and one concerning studies utilizing animals or *in vitro* systems (table A 25a). Although no consistent response was noted for serum cholesterol, serum free fatty acids were found consistently to rise following smoking. As with other cardiovascular reactions to nicotine and smoking, it appears that the fatty acid response is also mediated by catecholamine release. This relationship has been observed in a number of experiments by Kershbaum, et al. (*105, 106, 108, 109, 110*) and Klensch (*118*). That nicotine is primarily responsible for this rise may be seen by reference to the study by Kershbaum, et al. (*105*) in which lettuce-leaf cigarettes of minimal nicotine content had a negligible effect upon serum free fatty acids in comparison with that of regular cigarettes.

While attention has been centered upon nicotine as the agent inducing the immediate increase in serum lipids, recent studies have been concerned with the effect of chronic exposure to carbon monoxide on serum lipid metabolism. These studies are listed in table A 26. Among rabbits fed increased amounts of cholesterol, the authors observed significant increases in cholesterol and triglyceride concentrations in those exposed to CO versus those maintained in a normal atmosphere.

(105) Kershbaum, A., Bellet, S., Hirabayashi, M., Feinberg, L. J. Regular filtertip, and modified cigarettes. Nicotine excretion, free fatty acid mobilization and catecholamine excretion. Journal of the American Medical Association 201(7): 545–546, August 14, 1967.

(106) Kershbaum, A., Bellet, S., Jimenez, J., Feinberg, L. J. Differences in effects of cigar and cigarette smoking on free fatty acid mobilization and catecholamine excretion. Journal of the American Medical Association 195(13): 1095–1098, March 28, 1966.

(108) Kershbaum, A., Jimenez, J., Bellet, S., Zanettini, D. Modification of nicotine-induced hyperlipidemia by anti-adrenergic agents. Journal of Atherosclerosis Research 6: 524–530, 1966.

(109) Kershbaum, A., Khorsandian, R., Caplan, R. F., Bellet, S., Feinberg, L. J. The role of catecholamines in the free fatty acid response of cigarette smoking. Circulation 28(1): 52–57, July 1963.

(110) Kershbaum, A., Osada, H., Scriabine, A., Bellet, S., Pappas, D. J. Influence of nicotine on the mobilization of free fatty acids from rat adipose tissue *in vitro* and in the isolated perfused dog limb. Circulation 36(4, Supplement 2): 20, October 1967.

(118) Klensch, H. Blut-Katecholamine und -Fettsäuren beim Stress durch Rauchen und durch körperliche Arbeit. (Blood catecholamines and fatty acids under stress induced by smoke and exercise.) Zeitschrift für Kreislaufforschung 55(10): 1035–1044, October 1966.

Other Areas of Investigation

Certain other aspects of cardiovascular pathophysiology may be of importance in the relationship of smoking to CHD. Glucose metabolism and insulin response, when altered, may alter myocardial response. This topic has been covered in detail in the 1968 Supplement to the Health Consequences of Smoking (*192*). Also, variations in blood hemoglobin and hematocrit may adversely affect coronary blood flow. A number of studies showing a possible relationship of smoking to hemoconcentration have been reviewed previously (*191, 192*), and the reader is referred to those discussions.

2005050255

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

Cerebrovascular Disease

The term cerebrovascular disease (CVD) refers to a number of different types of vascular lesions affecting the central nervous system: subarachnoid hemorrhage, cerebral hemorrhage, cerebral embolism, and thrombosis (ICD Codes 330 to 334). In 1967 in the United States, a total of 93,071 males and 109,113 females were listed as dying from CVD as the underlying cause (*196*).

Epidemiological studies indicate that cigarette smoking is associated with increased mortality from cerebrovascular disease, whether CVD is listed as the underlying or as a contributory cause of death. Table 28 presents the results of the seven major epidemiological studies. The smoking of pipes and cigars does not appear to increase significantly the risk of dying from CVD. The importance of high blood pressure and diabetes as risk factors for mortality from CVD has recently been noted by Hammond and Garfinkel (*76*). The data from their study, as presented in table 28, also indicate that the mortality ratio for cigarette smokers is greater for persons under 75 years of age than for older individuals.

Many of the pathophysiological considerations discussed in the sections concerning CHD may also pertain to the relationship of smoking and CVD, particularly cerebral infarction.

In a study reported by Kuhn (*122*), 20 habitual smokers refrained from smoking for one-half day, and base line retrograde brachiocerebral angiograms were taken; they then smoked one cigarette, inhaling deeply, and had repeat angiograms. Those over 60 years of age failed to have significant acceleration of flow as demonstrated in carbon dioxide inhalation experiments.

More recently, Miyazaki (*132*) studied the effect of smoking on the cerebral circulation of 12 moderate/heavy cigarette smokers as measured indirectly using an ultrasonic Doppler technique to record internal carotid artery flow. Measurements were made before and after ordinary smoking and showed an increase in cerebral blood flow and a decrease in cerebral vascular resistance in all subjects. No significant difference in response was observed between the 4 younger and 8 older (over 60 years of age) subjects. More research is needed to clarify the role of cigarette smoking in the acute pathogenesis of CVD manifestations. However, the chronic effect of smoking upon the cerebral circulation (particularly its extracranial portion) is likely to be similar to the effect of smoking upon the aortic and coronary atherosclerosis.

(*122*) Kuhn, R. A. Mode of action of tobacco smoke inhalation upon the cerebral circulation. Annals of the New York Academy of Sciences 142 (Article 1): 67–71, March 15, 1967.

(*132*) Miyazaki, M. Circulatory effect of cigarette smoking, with special reference to the effect on cerebral hemodynamics. Japanese Circulation Journal 33(9): 907–912, September 1969.

Non-Syphilitic Aortic Aneurysm

Aortic aneurysm is an uncommon but not rare cause of death. In 1967 in the United States, a total of 8,448 men and 3,173 women were listed as dying from aortic aneurysm as the underlying cause (*196*). Cigarette smoking appears to increase the risk of dying from this disease, perhaps by promoting the atherosclerotic process which underlies this type of aneurysm. As illustrated in table 29, the mortality ratios for cigarette smokers are high relative to other cardiovascular diseases in which smoking increases the risk, and the risk increases in proportion to the amount smoked.

100505256

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

TABLE 24.—*Experiments concerning the atherogenic effect of carbon monoxide exposure and hypoxia*

Author, year, country, reference	Number and type of animal	Procedure	Results
Astrup et al., 1967 Denmark (10).	24 female albino rabbits.	Regular diet plus 2 percent cholesterol: I. (12) control. II. (12) continual exposure to carbon monoxide: 0.017 percent for 8 weeks. 0.035 percent for 2 weeks.	The experimental group exposed to carbon monoxide showed increased macro- and microscopic aortic atheromatosis over that shown by control animals. Microscopic examination revealed intimal lipoid deposition limited in penetration by the internal elastic membrane. Coronary vessels were found to show similar changes. Carboxyhemoglobin (COHb) levels averaged 15–17 percent during the first 6 weeks and 33 percent during the final 2 weeks.
Kjeldsen et al., 1968, Denmark (117).	24 castrated male albino rabbits.	Regular diet plus 2 percent cholesterol: I. (12) control. II. (12) continual exposure to hypoxia: 10 percent O_2 for 6 weeks. 8 percent O_2 for 2 weeks.	The experimental group exposed to hypoxia showed increased macroscopic aortic atheromatosis over that shown by control animals. Microscopic examination revealed more intimal and subintimal lipid deposition in the aortas of the exposed rabbits than in those of the nonexposed. The total amount of cholesterol deposited in the aortas of the experimental group was three times higher than in those of the control group.
Kjeldsen et al., 1969, Denmark (114).	24 castrated male albino rabbits.	Regular diet plus 2 percent cholesterol: I. (12) control. II. (12) exposure to 23 percent O_2 for 10 weeks.	Macroscopically, the experimental group showed significantly fewer atheromatous changes. Microscopically, the experimental group showed significantly less aortic intimal lipid deposition.
Webster et al., 1970, U.S.A. (204).	22 female squirrel monkeys.	Diet containing 0.5 percent cholesterol and 25 percent fat: I. (10) control. II. (12) experimentally exposed to 200–300 p.p.m. carbon monoxide for 20 hours per week for 7 months.	The experimental group exposed to carbon monoxide showed a greater mean percentage of coronary arteries with atherosclerotic lesions and more lumen occlusion among the affected arteries. There were significantly more CO-treated monkeys than control monkeys having 35 percent or more apparent atherosclerotic stenosis among the affected arteries. Aortic atherosclerosis was apparently not aggravated by exposure to CO. COHb levels at the end of each exposure period averaged 16–26 percent during the final 24 weeks of the experiment.

(117) KJELDSEN, K., WANSTRUP, J., ASTRUP, P. Enhancing influence of arterial hypoxia on the development of atheromatosis in cholesterol-fed rabbits. Journal of Atherosclerosis Research 8(5): 835–845. 1968.

(Mortality ratio—actual number of deaths shown in parentheses)[1]

[SM = smokers NS = nonsmokers]

PROSPECTIVE STUDIES

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of deaths due to CVD as underlying cause	Cigarettes per day	Pipes and cigars	Age variation	Comments
Hammond and Horn, 1958, U.S.A. (77, 78).	187,783 white males in 9 states 50–69 years of age.	Questionnaire and follow-up of death certificate.	8½	1,050	NS .....1.00 (166) Cigarettes SM .....†1.30 (656) Other SM ..1.25 (230) *Cigarettes only* <10 .....1.24 (41) 10–20 .....1.44 (140) >20 .....1.40 (83)			†($p<0.01$).
Doll and Hill, 1964, Great Britain (50).	Approximately 41,000 male British physicians.	Questionnaire and follow-up of death certificate.	10	606	NS .....1.00 All SM .....1.05 All cigarette 1.12 1–14 .....1.10 15–24 .....1.09 >25 .....1.26			
Kannel et al., 1965 U.S.A. (96).	5,127 males and females 30–59 years of age.	Medical examination and follow-up.	12	13	NS .....1.00 (5) Heavy SM (>20) 3.23 (8)			Data apply only to males 30–59 years of age at entry. Data apply only to cerebral infarction.

[1] Unless otherwise specified, disparities between the total number of deaths and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

(96) KANNEL, W. B., DAWBER, T. R., COHEN, M. E., MCNAMARA, P. M. Vascular disease of the brain—epidemiologic aspects. The Framingham study. American Journal of Public Health and the Nation's Health 55(9): 1355–1366, September 1965.

1005050757

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

TABLE 28.—*Deaths from cerebrovascular disease related to smoking (cont.)*

(Mortality ratios—actual number of deaths shown in parentheses)[1]

[SM = smokers NS = nonsmokers]

PROSPECTIVE STUDIES

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of deaths due underlying to CVD as cause	Cigarettes per day	Pipes and cigars	Age variation	Comments
Kahn, 1966, U.S.A. (83).	U.S. male veterans 2,285,674 person years.	Questionnaire and follow-up of death certificate.	8½	2,038	NS .....1.00 (614) All current ....1.30(1,534) Current cigarettes ..1.52 (692) 1–9 .....1.51 (93) 10–20 .....1.42 (325) 21–39 .....1.70 (216) >39 .....1.59 (37)	*Pipes* SM ..1.06 (82) NS ..1.00(614) *Cigars* NS ..1.00(614) SM ..1.03(135)		—
Hammond and Garfinkel, 1969, U.S.A. (76).	358,534 males 465,875 females 40–79 years of age at entry.	Questionnaire and follow-up of death certificate.	6	4,039			*Current regular cigarette* 40–49 50–59 60–69 70–79 *Males* Never smoked 1.00 1.00 1.00 1.00 1–9 .....2.78 1.85 1.50 0.95 10–19 .....1.14 1.48 †1.46 0.92 20–39 .....2.21 2.03 1.62 1.22 >40 .....1.64 2.40 1.72 †0.68 *Females* Never smoked 1.00 1.00 1.00 1.00 1–9 .....1.53 1.26 1.26 0.83 10–19 .....2.60 2.70 2.15 †0.67 20–39 .....2.93 2.67 1.83 1.28 >40 .....†5.70 †3.52 — —	†Based on only 8–9 deaths.

[1] Unless otherwise specified, disparities between the total number of deaths and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

TABLE 28.—*Deaths from cerebrovascular disease related to smoking (cont.)*

(Mortality ratios—actual number of deaths shown in parentheses)[1]

SM = Smokers. NS = Nonsmokers.

PROSPECTIVE STUDIES

Paffenbarger, et al. 1970 U.S.A. (144).	3,263 male longshoremen 35–64 years of age in 1951.	Initial multiphasic screening and follow-up of death certificate.	16	47	NS and <20 .....1.00 (42) >20 .....1.15 (25)		

RETROSPECTIVE STUDY

Paffenbarger and Williams 1967 U.S.A. (145).	>50,000 male University students followed up to 60 years.	Initial college entrance medical examinations with follow-up of death certificate. Controls—surviving classmates age-matched.		*Death Rates* *Cases (158)*	*Controls (615)*	The 63 deaths from occlusive stroke contributed to the statistical significance. The 95 deaths from hemorrhagic stroke showed no statistical significance as a single group.
			SM	45.0	31.3 ($p<0.01$)	
			Cigarette SM >10 per day .	20.9	11.2 ($p<0.01$)	

[1] Unless otherwise specified, disparities between the total number of deaths and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

(145) PAFFENBARGER, R. S., JR., WILLIAMS, J. L. Chronic disease in former college students. V. Early precursors of fatal stroke. American Journal of Public Health and the Nation's Health 57(8): 1290–1299, August 1967.

100505058

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

TABLE 29.—*Deaths from nonsyphilitic aortic aneurysm related to smoking—prospective studies*

(Mortality ratios—actual number of deaths shown in parentheses)[a]

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Data collection	Follow-up years	Number of deaths	Cigarettes per day	Pipes	Cigars	Comments
Hammond and Horn, 1958, U.S.A. (*77, 78*).	187,783 white males in 9 states 50–69 years of age.	Questionnaire and follow-up of death certificate.	3½	66	NS .....1.00 (25) (expected) SM .....2.12 (44) ($p<0.006$)			
Kahn, 1963, U.S.A. (*88*).	U.S. male veterans 2,365,874 person years.	Questionnaire and follow-up of death certificate.	8½	421	NS .....1.00 (15) Current cigarettes ....2.24 (234) 1–9 cigarettes/day ....2.12 (13) 10–20 .....2.53 (124) 21–39 .....4.86 (76) ≥39 .....7.26 (17)	NS ..1.00 (85) SM ..1.38 (8)	NS ..1.63 (65) SM ..2.96 (54)	
Hammond and Garfinkel, 1969, U.S.A. (*76*).	248,334 males 443,325 females 40–79 years of age at entry.	Questionnaire and follow-up of death certificate.	6	337	NS .....1.00 1–9 .....2.65 10–19 .....3.85 20–39 .....4.84 ≥40 .....5.00			Data apply only to males 50–69 years of age.
Weir and Dunn, 1970, U.S.A. (*203*).	68,357 California male workers 35–64 years of age at entry.	Questionnaire and follow-up of death certificate.	5–8	61	NS .....1.00 ≤5 .....2.64 ≥10 .....2.44 ≥20 .....2.88 ≥30 .....2.64			SM include ex-smokers. NS include pipe and cigar smokers.

[a] Unless otherwise specified, disparities between the total number of deaths and the sum of the individual categories are due to the exclusion of other occasional, miscellaneous, mixed, or ex-smokers.

PERIPHERAL ARTERIOSCLEROSIS

Peripheral arteriosclerosis represents the effects on the vasculature of the extremities of the pathophysiologic processes which produce coronary and aortic atherosclerosis. A number of studies have been concerned with smoking as a risk factor in the development of this disease. Kannel, et al. (*95*) observed, in the Framingham study, that diabetes mellitus and elevated serum cholesterol, as well as cigarette smoking, were also risk factors in the development of peripheral vascular disease.

Juergens, et al. (*92*) reviewed the records of and contacted 478 male patients with arteriosclerosis obliterans (a severe form of peripheral arteriosclerosis), who had been patients at the Mayo Clinic between 1939 and 1948. The diagnosis of this condition was based upon certain clinical criteria: the presence of intermittent claudication, the marked diminution or absence of lower extremity arterial pulsations, and objective trophic manifestations of peripheral limb ischemia. Smoking information was available on 401 patients. These patients were compared with a control group of 350 Mayo Clinic patients of similar age who showed no clinical evidence of vascular disease. It was found, for males under the age of 60, that 2.5 percent of the cases and 25 percent of the controls were nonsmokers. However, no difference was noted between the percentages of heavy smokers in each group. The authors also implicated high blood pressure and elevated serum cholesterol as risk factors in the occurrence of this disease.

Begg (*19*) noted similar findings in a study of 204 male patients with intermittent claudication who were patients at the Western Infirmary in Glasgow, Scotland. In comparing the smoking histories of 100 patients with this complaint with those of 116 healthy male controls, the author found that 1 percent of the patients and 21 percent of the controls had never smoked. A total of 42 percent of the patients smoked more than 20 cigarettes per day while only 24 percent of the controls had a similar history of heavy smoking. The author concluded that smoking, while not a prime cause of peripheral arterial disease, is a significant cofactor in its development in almost all cases. The author also noted obesity, high blood pressure, and elevated serum cholesterol as risk factors.

(*95*) KANNEL, W. B., DAWBER, T. R., SKINNER, J. J., JR., MCNAMARA, ... SHURTLEFF, D. Epidemiological aspects of intermittent claudication: The Framingham Study. Circulation (Supplement II to Vols. 31 ... 32): 121–122, October 1965.

(*92*) JUERGENS, J. L., BARKER, N. W., HINES, E. A., JR. Arteriosclerosis ... literans: Review of 520 cases with special reference to pathogen... and prognostic factors. Circulation 21(2): 188–195, February 195...

(*19*) BEGG, T. B. Characteristics of men with intermittent claudica... Practitioner 194(2): 202–207, February 1965.

10050759

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

Schwartz, et al. (*168*) compared the prevalence of risk factors in four groups of subjects: 141 cases with arteriosclerotic disease of the lower limbs, 551 cases with coronary arteriosclerosis, 58 cases with both conditions, and finally an indefinite number of control individuals who had been hospitalized for injuries. The investigators reported that certain risk factors, including hypercholesterolemia, hypertension, and cigarette smoking, were significant in both coronary and lower limb arteriosclerosis. The authors noted that the inhalation of cigarette smoke appeared to be an important risk factor for coronary arteriosclerosis up to age 55 while in arteriosclerosis of the lower extremities, inhalation appeared to increase the risk even in the older age groups.

(168) SCHWARTZ, D., LELLOUCH, J., ANGUERA, G., RICHARD, J. L., BEAUMONT, J. L. Etiologie comparee de l'arteriopathie obliterante des membres inferieurs et de l'arteriopathie coronarienne. (Comparative etiology of lower limb obliterative arteriopathy and of coronary arteriopathy.) Archives des Maladies du Coeur 58: Supplement No. 3, 24–32, 1965.

Widmer, et al. (*215*) compared 277 male patients with arterial occlusion of the limbs as demonstrated by aortography or oscillography with 2,082 men demonstrated by oscillography to be free of arterial disease. The authors found that cigarette smoking, particularly heavy smoking, was significantly more frequent among the cases with arterial occlusion than among the controls. Increased beta-lipoproteins and systolic hypertension were also found to be more common among the cases.

(215) WIDMER, L. K., HARTMANN, G., DUCHOSAL, F., PLECHL, S.-C. Risk factors in arterial occlusion of the limbs. German Medical Monthly 14 (10): 476–479, October 1969.

EXPERIMENTAL EVIDENCE

A number of experimenters have investigated the acute effects of smoking or nicotine upon the peripheral circulatory system. These investigators, as listed in table A 30, have measured effects in terms of alterations in skin temperature and blood flow as measured by plethysmography, radioactive iodinated albumin clearance, or radiosodium clearance from the skin. The majority of these studies have shown significant decreases in peripheral blood flow and skin temperature upon smoking, particularly in persons without manifest peripheral vascular disease. The study of Freund and Ward (*68*) demonstrates the difference in peripheral vascular reactivity found between normals and patients with arteriosclerotic changes in the vessels of their extremities. The work of Stromblad (*181*) on blockade of this response with automatic system blockers indicates that the reactivity of these vessels is secondary to the local release of catecholamines. Most probably, the degenerative changes associated with this disease create a stiffening of the vessel wall and prevent rapid alteration, particularly dilatation, in response to the catecholamines liberated by smoking or nicotine.

(68) FREUND, J., WARD, C. The acute effect of cigarette smoking on the digital circulation in health and disease. Annals of the New York Academy of Sciences 90(1): 85–101, September 27, 1960.

(181) STROMBLAD, B. C. R. Effect of intra-arterially administered nicotine on the blood flow in the hand. British Medical Journal 1: 484–435, February 21, 1959.

1005050760

THROMBOANGIITIS OBLITERANS

Thromboangiitis obliterans (Buerger's Disease) (TAO) is an uncommon obstructive vasculitis primarily involving the arteries and veins of the extremities. Severely affected patients may even lose their limbs secondary to ischemic changes. Much discussion has centered upon the question as to whether this disease is a clinical and pathological entity separate from peripheral arteriosclerosis. McKusick, et al. (*123*) consider it to be a distinct entity while Eisen (57) concludes that TAO is the acute inflammatory phase of severe arteriosclerosis.

Clinically, it has been shown that smoking aggravates this disease and cessation of smoking frequently aids in complete or partial remission. Razdan, et al. (*153*) and Brown, et al. (*32*) found very few nonsmokers in groups of patients diagnosed as having typical TAO. A recent study from Israel (*16*) involved a case-control comparison of 46 patients with TAO and 32 matched controls. Although the controls were found to smoke less per day than the patients, this difference was not found to be statistically significant. However, 100 percent of the smoking patients and only 72 percent of the smoking controls were inhalers, a difference significant at the 0.02 level.

(123) MCKUSICK, V. A., HARRIS, W. S., OTTESEN, O. E., GOODMAN, R. M., SHELLEY, W. M., BLOODWELL, R. D. Buerger's disease: A distinct clinical and pathologic entity. Journal of the American Medical Association 181(1): 5–12, July 7, 1962.

(57) EISEN, M. E. Coexistence of thromboangiitis obliterans and arteriosclerosis: Relationship to smoking. Journal of the American Geriatrics Society 14 (8): 846–858, August 1966.

(153) RAZDAN, A. N., SINGH, R. P., SRIVASTAVA, V. K. Thromboangiitis obliterans. A clinical study of 125 cases. International Surgery; Bulletin 47(2): 122–125, February 1967.

(32) BROWN, H., SELLWOOD, R. A., HARRISON, C. V., MARTIN, P. Thromboangiitis obliterans. British Journal of Surgery 56 (1): 59–63, January 1969.

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

Site of Action of Nicotine. The last sentence of the paragraph was not made by (181) Stromblad. As a matter of fact, Stromblad was not certain that nicotine caused the release of catecholamines and could not exclude a second mechanism. The 1971 document wants to protect the concept that nicotine primarily causes a release of catecholamines at the blood vessels.

Discussion

Nicotine has been thought to cause a peripheral vasoconstriction by way of the sympathetic nervous system. The present report shows that nicotine causes an immediate vasoconstriction in the human hand when injected into the brachial artery. This effect is likely to be due to a direct peripheral action of nicotine, especially as vasoconstrictor responses were absent from the contralateral hand.

According to the calculations of Boyle *et al.* (1947), based on the findings of Baumberger (1923), smoking of cigarettes with inhalation will give an absorption of nicotine equivalent to 2 mg. of nicotine bitartrate a minute. The flow in the brachial artery at the site used for infusion may be about one-hundreth of the cardiac output, and hence smoking would correspond to an infusion of some 20 μg./min. in this artery. In the present experiments this was just about the threshold dose for vasoconstriction in certain individuals. Moreover, it is quite possible that during prolonged smoking there may be an accumulation of nicotine in the blood, causing a higher dosage than calculated above. It is therefore likely that in some individuals the amount of nicotine absorbed during smoking is big enough to elicit a direct peripheral effect. These assumptions and calculations are not necessarily contradictory to earlier reports that sympathetic blockade abolishes the vascular effect of smoking, since there are great individual variations in sensitivity, and the early experiments with sympathetic blocking were made in only a few cases.

The mechanism of the peripheral action of nicotine is not known. However, the present observation that sympathicolytic agents prevent the vascular effect of nicotine is compatible with the assumption that nicotine acts by release of sympathicomimetic substances (for references see Burn and Randl, 1958). These substances may be released from the system of chromaffin cells lying close to the small vessels of the human skin (Adams-Ray and Nordenstam, 1956) or they could be released from the store which has been found in the arterial walls (Schmiterlow, 1948). A release from a chromaffin system would be consistent with the finding that ganglion-blocking agents prevent the effect of nicotine.

Another possible mechanism of the peripheral action of nicotine would be by excitation of a peripheral nervous plexus containing ganglion cells and adrenergic terminals. But so far no such peripheral nervous plexus has been definitely demonstrated (Folkow, 1956).

Summary

Nicotine was found to cause vasoconstriction in the hand when injected into the brachial artery. The threshold doses varied greatly between individuals, but, at least in some, the amount of nicotine assumed to be absorbed during smoking would be enough to cause vasoconstriction via a local mechanism. Sympathicolytics and ganglion-blocking agents abolished the effect of nicotine. This appears consistent with the assumption that nicotine causes a release of sympathicomimetics from the chromaffin system in the human skin, but could also be explained by the existence of a peripheral nervous plexus containing ganglion cells.

100505076

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

CARDIOVASCULAR DISEASES

SUMMARY AND CONCLUSIONS

Coronary Heart Disease

1. Data from numerous prospective and retrospective studies confirm the judgment that cigarette smoking is a significant risk factor contributing to the development of coronary heart disease including fatal CHD and its most severe expression, sudden and unexpected death. The risk of CHD incurred by smokers of pipes and cigars is appreciably less than that by cigarette smokers.

2. Analysis of other factors associated with CHD (high serum cholesterol, high blood pressure, and physical inactivity) shows that cigarette smoking operates independently of these other factors and can act jointly with certain of them to increase the risk of CHD appreciably.

3. There is evidence that cigarette smoking may accelerate the pathophysiological changes of pre-existing coronary heart disease and therefore contributes to sudden death from CHD.

4. Autopsy studies suggest that cigarette smoking is associated with a significant increase in atherosclerosis of the aorta and coronary arteries.

5. The cessation of smoking is associated with a decreased risk of death from CHD.

6. Experimental studies in animals and humans suggest that cigarette smoking may contribute to the development of CHD and/or its manifestations by one or more of the following mechanisms:

a. Cigarette smoking, by contributing to the release of catecholamines, causes increased myocardial wall tension, contraction velocity, and heart rate, and thereby increases the work of the heart and the myocardial demand for oxygen and other nutrients.

b. Among individuals with coronary atherosclerosis, cigarette smoking appears to create an imbalance between the increased needs of the myocardium and an insufficient increase in coronary blood flow and oxygenation.

c. Carboxyhemoglobin, formed from the inhaled carbon monoxide, diminishes the availability of oxygen to the myocardium and may also contribute to the development of atherosclerosis.

d. The impairment of pulmonary function caused by cigarette smoking may contribute to arterial hypoxemia, thus reducing the amount of oxygen available to the myocardium.

e. Cigarette smoking may cause an increase in platelet adhesiveness which might contribute to acute thrombus formation.

Cerebrovascular Disease

1. Data from numerous prospective studies indicate that cigarette smoking is associated with increased mortality from cerebrovascular disease.

2. Experimental evidence concerning the relationship of smoking and cerebrovascular disease is at present insufficient to allow for conclusions concerning pathogenesis. However, some of the pathophysiological considerations discussed concerning CHD may also pertain to the relationship of smoking and CVD, particularly cerebral infarction.

Non-Syphilitic Aortic Aneurysm

Cigarette smoking has been observed to increase the risk of dying from nonsyphilitic aortic aneurysm.

Peripheral Vascular Disease

1. Data from a number of retrospective studies have indicated that cigarette smoking is a likely risk factor in the development of peripheral vascular disease. Cigarette smoking also appears to be a factor in the aggravation of peripheral vascular disease.

2. Cigarette smoking has been observed to alter peripheral blood flow and peripheral vascular resistance.

10050762

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

Conclusion. After the appearance of the 1971 Document, Seltzer wrote a letter to the New England Journal of Medicine (288: 1186, 1973).

SMOKING AND CORONARY HEART DISEASE

To the Editor: In many, but not all, countries, cigarette smokers have been found to have higher rates of coronary heart disease than nonsmokers.[1] Even though dose-response relations and data on former cigarette smokers show a number of inconsistencies,[2,3] cigarettes have been accepted by the Public Health Service as "one of the major risk factors contributing to the development of . . . [coronary heart disease]."[3]

One of the particular strengths cited in governmental statements on cigarettes and lung cancer has been the interpretation of secular changes in lung-cancer mortality among British doctors, likening it to "that of a controlled cessation experiment."[4] As shown in Table 1,[5] mortality from this cause decreased by 25 per cent over a 12-year period in which the prevalence of cigarette smokers in the same population decreased by close to 50 per cent.

Table 1. Mortality from Lung Cancer and Coronary Heart Disease (CHD) among British Doctors 35 to 84 Years of Age.[5]

Prevalence of Cigarette Smokers		Age-Standardized Mortality (Rates/1000/Yr)		
yr	%	*period*	*lung cancer*	*CHD*
1951	41.3	1953-57	1.10	5.19
1957	32.9	1957-61	0.85	5.64
1966	21.3	1961-65	0.83	5.59
		% *change*		
		1st-2d period	−23	+9
		2d-3d period	− 2	−1
		1st-3d period	−25	+8

Now, if cigarette smoking were indeed clearly linked to coronary heart disease, by the same logic one would have expected to find a decrement in mortality from this cause over this period also. But inspection of these data (Table 1) reveals that, instead of decreasing, mortality actually increased by some 8 per cent.

Thus, the type of epidemiologic observations that provided the basis for the statement, "the reduction of rates experience in ex-smokers . . . is clearly shown in the case of lung cancer to be a reflection of significant change in risk,"[4] lends no support to the current enthusiasm for cigarette smoking as a major risk factor in coronary heart disease.

Carl C. Seltzer, Ph.D.
Harvard School of Public Health
Boston, Mass.

10050763

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

(60) ENGLISH, J. P., WILLIUS, F. A., BERKSON, J. Tobacco and coronary disease. Journal of the American Medical Association 115(16): 1327–1329, October 19, 1940.

(131) MILLS, C. A., PORTER, M. M. Tobacco smoking and automobile-driving stress in relation to deaths from cardiac and vascular causes. American Journal of the Medical Sciences 234(1): 35–43, July 1957.

(33) BUECHLEY, R. W., DRAKE, R. M., BRESLOW, L. Relationship of amount of cigarette smoking to coronary heart disease mortality rates in men. Circulation 18(6): 1085–1090, December 1958.

TABLE A6.—*Coronary heart disease morbidity and mortality—retrospective studies*

(Actual number of cases shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers EX = Ex-smokers]

Author, year, country, reference	Number and type of population	Data collection	Cases (percent)	Controls (percent)	Comments
English et al., 1940, U.S.A. (60).	1,000 males with manifest CHD, 40 years of age. Controls: 1,000 male non-CHD patients.	Case selection from Mayo Foundation files. Controls: same year of admission age-matched.	*Age* *Percent Smokers* 40–49 .....79.7 (187) 50–59 .....71.7 (392) 60 or over .....63.8 (431) All ages 69.8	*Percent Smokers* 61.9 (302) ($p<0.001$) 78.9 (371) (not significant) 61.8 (327) (not significant) 66.3 ($p<0.05$)	
Mills and Porter, 1957, U.S.A. (131).	474 white male coronary deaths. Controls: 605 white males.	Undefined.			
			40–49 *50–59* *60–69* *70 or over*	*40–49* *50–59* *60–69* *70 or over*	
			(66) (135) (153) (130)	(216) (188) (114) (88)	
			NS 7.14 6.66 19.30 33.84	19.91 24.47 35.09 64.12	
			All cigarettes 83.93 82.23 47.02 15.44	70.83 59.04 43.86 16.47	
			Pipes, cigars 8.93 11.11 32.63 47.70	9.26 16.47 21.05 29.41	
Buechley et al., 1958, U.S.A. (33).	Males reporting CHD to California Health Survey, with matched controls from same survey (included those surviving first myocardial infarction).	Questionnaire and interview.	NS .....20.4 (23) ≤20 .....61.1 (69) >20 .....18.6 (21)	NS .....42.1 (51) ≤20 .....45.5 (55) >20 .....11.6 (14)	

1005050764

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

TABLE A6.—*Coronary heart disease morbidity and mortality—retrospective studies (cont.)*

(Actual number of cases shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers EX = Ex-smokers]

Author, year, country, reference	Number and type of population	Data collection	Cases (percent)	Controls (percent)	Comments
Russek and Zohman, 1958, U.S.A. (163).	97 male and 3 female coronary patients. Controls: 100 healthy controls of similar age, sex, occupation, and ethnic origin.	Interviews by authors.	*Tobacco usage>20 cigarettes/day* 70 percent.	35 percent.	Patients included 89 with classic myocardial infarction and 11 with angina pectoris.
Spain and Nathan, 1961, U.S.A. (174).	269 males identified as having CHD by physical examination and history. Controls: 2,637/3,000 males identified as not having CHD	3,000 males in New York City interviewed and examined by medical group.	NS .....20.0 (81) <40/day .....29.0 (78) >40/day .....13.0 (33) EX .....14.0 (38) Cigar, pipe .....14.0 (36) Total .....100.0(269)	29.0 (772) 33.0 (876) 9.0 (234) (p<0.05) 14.0 (361) 15.0 (400) 100.0(2,637)	
Mulcahy and Hickey, 1967 Ireland (135, 136).	403 men less than 60 years of age with classical CHD. Data compared with male population consumption figures.	Interview.	*Males* NS ..... 4.60 (18) SM .....89.75(362) EX ..... 4.75 (19) Total .....100.00(400)	*Males* 18.2(118) 76.6(427) 11.2 (68) 106.0(613)	Control smoking data obtained from estimated smoking habits of Irish population of same age group.
Schwartz et al., 1966, France (169).	612 male patients with angina or myocardial infarction. 612 age-matched controls.	Interview, laboratory, and clinical examinations.	Average amount per day as cigarettes .....18.6 All SM .....86.0 Inhalers 69.0	15.6 (p<0.0001) 86.0 46.0(p<0.00001)	Data apply only to those under 55 years of age.

TABLE A6.—*Coronary heart disease morbidity and mortality—retrospective studies (cont.)*

(Actual number of cases shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers EX = Ex-smokers]

Author, year, country, reference	Number and type of population	Data collection	Cases (percent)			Controls (percent)		Comments
			Males (72)	*Females* (21)	*Males* (72)	*Females* (84)		
Villiger and Heyden-Stucky, 1966, Switzerland (201).	103 cases with recent myocardial infarction. 72 males, 25 females, 100 age-matched controls (72 male industrial employees and 28 females in hospital for other diagnoses).	Hospital history or interview.	NS 4.94	32.4	†21.0	82.1		These are not pure smoking classes. †(p<0.01)
			Cigarette 66.7	28.6	46.0	14.3		
			1–19 cigarettes/day 18.1	10.7	22.0	10.7		
			>20 ..... 48.6	17.9	†22.2	3.6		
			Cigar, pipe 44.4	...	27.5	..		
			EX 4.2	...	†18.5	3.6		
Dörken, 1967, Germany (53).	385 males up to 44 years of age with myocardial infarction or sudden death (133 deceased, 66 living). Controls—Hamburg age-matched citizens selected randomly.	Death certificate review. Interview of patient or kin.	NS 1.0 (2)			18.4 (74)		Ex-smokers listed under nonsmokers. Smoking information available only on 199/385. Three cigarette cate-gories include mixed or cigar smokers recalculated as to number of cigarettes. No patients or controls smoked pipes exclusively.
			Cigarette Units					
			1–6 ..... 1.5 (3)			10.0 (43)		
			10–16 .....32.3 (62)			46.5(192)		
			20–30 .....43.6 (84)			22.5 (93)		
			>35 .....21.2 (42)			2.5 (9)		
			100.0(193)			106.0(413)		
			(only 28 were mixed or cigar smokers)			(62 were mixed or cigar smokers)		
Dörken, 1967, Germany (53).	83 females up to 44 years of age with myocardial infarction or sudden death. Controls—133 females 21–44 years of age from clinic without CVD or lung cancer.	Death certificates, interviews.	*Cigarettes per day* 0 ..... 6.1 (8)			55.2(84) (p<0.001)		
			1–5			17.8(23)		
			6–15 .....48.6 (16)			16.5(22)		
			20–30 .....30.4 (10)			3.0 (4)		
			>35 ..... 6.1 (2)			...		

(163) RUSSEK, H. I., ZOHMAN, B. L. Relative significance of heredity, diet and occupational stress in coronary heart disease of young adults. Based on an analysis of 100 patients between the ages of 25 and 40 years and a similar group of 100 normal control subjects. American Journal of the Medical Sciences 235(3): 266–277, March 1958.

(174) SPAIN, D. M., NATHAN, D. J. Smoking habits and coronary atherosclerotic heart disease. Journal of the American Medical Association 177 (10): 637–683, September 9, 1961.

(135) MULCAHY, R., HICKEY, N. J. Cigarette smoking habits of patients with coronary heart disease. British Heart Journal 28: 401–408, 1966.

(136) MULCAHY, R., HICKEY, N. J. The role of cigarette smoking in the causation of atherosclerosis. Geriatrics 22(2): 165–174, February 1967.

(169) SCHWARTZ, D., LELLOUCH, J., ANGUERA, G., BEAUMONT, J. L., LENEGRE, J. Tobacco and other factors in the etiology of ischemic heart disease in man: Results of a retrospective survey. Journal of Chronic Diseases 19(1): 35–55, January 1966.

(201) VILLIGER, U., HEYDEN-STUCKY, S. Das Infarktprofil. Unterschiede zwischen infarktpatienten und Kontrollpersonen in der Ostschweiz. (The infarct profile. Differences between infarct patients and controls in East Switzerland.) Schweizerische Medizinische Wochenschrift 96(23): 748–758, June 11, 1966.

(53) DÖRKEN, H. Die Rauchgewohnheitenbei jüngeren Herzinfarkt-Patienten. (Smoking habits of younger patients with myocardial infarction.) Munchener medizinische Wochenschrift 109(4): 187–192 January 27, 1967.

(53) DÖRKEN, H. Die Rauchgewohnheiten bei jüngeren Frauen mit Herzinfarkt. (The smoking habits of younger females with myocardial infarction.) Munchener medizinische Wochenschrift 109(41): 2129 2134, October 13, 1967.

10050765

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

TABLE A6.—*Coronary heart disease morbidity and mortality—retrospective studies (cont.)*

(Actual number of cases shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers EX = Ex-smokers]

Author, year, country, reference	Number and type of population	Data collection	Cases (percent)	Controls (percent)	Comments
Hyams et al., 1967, Japan (87).	73 males surviving myocardial infarction. 157 age-matched controls hospitalized for non-CVD but include hypertensive disease.	Interviews by trained personnel.	NS .....10.1 (8) 1-9 cigarettes per day ..... 7.0 (5) 10-15 .....25.4 (18) 16-20 .....35.2 (25) 21-24 .....22.5 (16) >25 ..... 9.9 (7) All SM 100.0 (71)	21.0 (33) 10.6 (15) 23.0 (42) 25.5 (32) 17.7 (22) 12.1 (16) 100.0(324)	
Mulcahy et al., 1967, Ireland (137).	100 female patients less than 60 years of age admitted to hospital with CHD.	Hospital interviews.	SM .....63.0 (63) NS .....33.0 (33) EX ..... 4.0 (4) Total .....100.0(100)	45.6 (261) 44.3 (259) 9.1 (52) 100.0(572)	Smoking on controls obtained from statistics of smoking in Irish Republic. Sudden death not included.
Stejfa, 1967, Poland (178).	70 male and female patients with recent onset exertional angina pectoris. 54 controls of same age.	Direct interviews.	*Prevalence of risk factors* *Angina patients* 60.0	*Control group* 48.1(p>0.1)	Authors then followed the 70 patients for 3 years and noted that smoking significantly influenced the incidence of coronary occlusion.
Schimmler et al., 1968, Germany (167).	503 males with healed myocardial infarctions. 714 male controls of same age without detectable heart disease.	Hospital interviews.	NS .....9.0 (44) EX .....12.0 (69) Cigar, pipe .....12.0 (62) <19 cigarettes ....25.0(129) >20 .....42.0(209) Total .....100.0(503)	26.0(187) (p<0.001) 20.0(142) (p<0.001) 11.0 (77) 24.0(191) (p<0.001) 29.0(207) (p<0.001) 100.0(714)	

TABLE A6.—*Coronary heart disease morbidity and mortality—retrospective studies (cont.)*

(Actual number of cases shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers EX = Ex-smokers]

Author, year, country, reference	Number and type of population	Data collection	Cases (percent)	Controls (percent)	Comments
Hood et al., 1969, Sweden (85).	230 males surviving early first myocardial infarction. Controls: 855 randomly selected males 50 years of age.	Interview and examination.	(230) Never smoked ....1.7% EX before infarction .....1.7% EX after infarction .....29.1 <15 cigarettes ...28.3 >15 cigarettes ...22.6 All .....80.0 Pipe 16.5	(855) 24.3 30.7 -- 27.4 24.0 47.4 8.8	
Jouve et al., 1969, France (91).	1,229 CHD patients: 802 males, 427 females. Controls: 743 individuals of both sexes: age, sex, and social class matched.	Interview.	43.0	33.0(p<0.0001)	
Kastl, 1969, Germany (94).	273 male railway employees up to 65 years of age surviving myocardial infarction. 275 control employees with minor circulatory disturbances.	Interview and examination.	NS .....20.0 (55) 2-20 cigarettes or up to 6 cigars. ...32.0 (88) >20 cigarettes or >6 cigars. .....48.0(132)	29.5 (82) 63.3 (83) 6.5 (99)	

[1] Unless otherwise specified, disparities between the total number of cases and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

(87) HYAMS, L., SEGI, M., ARCHER, M. Myocardial infarction in the Japanese. A retrospective study. American Journal of Cardiology 20(4): 549–554, October 1967.

(137) MULCAHY, R., HICKEY, N. J., MAURER, B. J. Coronary heart disease in women. Study of risk factors in 100 patients less than 60 years of age. Circulation 36(4): 577–589, October 1967.

(178) STEJFA, M., JR. Predictive significance of risk factors in exertional angina pectoris. Cardiologia 51(6): 330–339, 1967.

(167) SCHIMMLER, W., NEFF, C., SCHIMERT, G. Risikofaktoren und Herzinfarkt. Eine retrospektive studie. (Risk factors and myocardial infarct. A retrospective study.) Munchener Medizinische Wochenschrift 110(27): 1585–1594, July 5, 1968.

(85) HOOD, B., TIEMLIN, G., WELIN, G., ORNDAHL, G., KORSAN-BENGTSEN, K. Myocardial infarction in early age. III. Coronary risk factors and their deficient control. Acta Medica Scandinavica 185(4): 241–251, April 1969.

(91) JOUVE, A., ROCHU, P., AVRIL, P. Enquetes epidemiologiques sur l'atherosclerose dans la region Provencale. (Epidemiological investigations of atherosclerosis in the Provence region.) Union Medicale du Canada 98(5): 761–765, May 1969.

(94) KASTL, O. Berufliche und Umweltanalyse infarktkranker Eisenbahnbediensteter. (Occupational and environmental analysis of infarct patients in railway service.) Medizinische Klinik 64(42): 1911–1917, October 17, 1969.

1005050766

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

TABLE A7.—*Differences in serum lipids between smokers and nonsmokers (cont.)*

(Actual number of individuals shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results	Comments
Acheson and Jessop, 1961 Ireland (1).	221 randomly chosen pensioners 65–85 years of age.	*Mean serum cholesterol mg. percent* / *Mean Beta/Alpha lipoprotein ratio* NS ..... 214(33) / 2.0(36) 5 cigarettes/day ..... 201(12) / 2.1(11) 10 ..... 213(34) / 1.9(33) 20 ..... 221(33) / 1.9(25) >30 ..... 206 (8) / 1.8 (8)	
Bronte-Stewart, 1961, South Africa (31).	Approximately 600 healthy males 25–55 years of age.	*Cholesterol mg. percent*: 25–39 †A ‡E; 40–55 A E NS ..... 179 197 222 245 "Heavy" SM .. 156 223 204 256 *Beta/Alpha lipoprotein ratio*: 25–39 A E; 40–55 A E NS ..... 3.83 3.84 3.75 4.69 "Heavy" SM .. 3.82 4.40 4.07 5.40	No data given on numbers in each group. †A—African. ‡E—European.
Konttinen, 1962, Finland (119).	314 male military recruits 18–25 years of age.	*Serum cholesterol mg. percent* / *Serum phospholipide mg. percent* NS .....(145)..... 203.8 / 218.0 (Cigarettes per day) 1–10 (53)..... 206.8 / 222.3 11–19 .....(64)..... 215.1 / 224.7 >20 .....(62)..... 202.3 / 210.5	No serum lipid differences found among the various smoking groups.
Blomstrand and Lundman, 1966, Sweden (26).	76 monozygotic twin pairs and 87 dizygotic twin pairs obtained from Swedish Twin Registry.	I. Monozygotes discordant for smoking: Smokers showed slightly lower levels of cholesterol, triglycerides, and phospholipids than nonsmokers. II. Dizygotes discordant for smoking: Smokers showed significantly higher levels of phospholipids. No differences for cholesterol and triglycerides.	The authors conclude from the differing MZ and DZ results that constitutional factors are probably more important than smoking in determining lipid levels.

TABLE A7.—*Differences in serum lipids between smokers and nonsmokers*

(Actual number of individuals shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results	Comments
Gofman et al., 1955, U.S.A., (72).	401 male employees 20–59 years of age.	*Difference between SM and NS* Lipid: / *Ages 20–29* (NS 66, SM 37) / *Ages 30–39* (NS 56, SM 67) / *Ages 40–59* (NS 17, SM 44) ‡Sf 0–12 ..... +59.9 p<0.001 / +19.9 p<0.05 / + 3.9 p<0.05 Sf 12–20 ..... + 9.4 p<0.001 / + 5.4 p<0.05 / − 3.6 p<0.05 Sf 20–100 ..... +20.0 p<0.025 / + 9.1 p<0.05 / + 8.5 p<0.05 Sf 100–400 ..... +15.8 p<0.025 / +12.1 p<0.05 / − 4.5 p<0.05 Cholesterol ..... +21.2 p<0.05 / + 9.0 p<0.05 / − 4.8 p<0.05	‡Sf refers to Svedberg flotation units of centrifuged lipoproteins.
Thomas, 1958, U.S.A. (185).	521 medical students.	*Serum cholesterol mg. percent* *NS (264)* Observed/Expected / *SM (257)* Observed/Expected <250 ..... 170/157 / 149/161.6 >250 ..... 87/99.6 / 116/102.4 Chi Square Value = 8.2 p<0.025	
Dawber et al., 1959, U.S.A. (47).	2,253 males participating in the Framingham study 29–59 years of age.	*Serum cholesterol mg. percent* *30–44* / *45–59* NS ..... 216.1(149) / 228.3(131) All cigarettes ..... 224.8(674) / 229.5(589) <10 ..... 217.4 (76) / 229.1 (76) 10–19 ..... 221.1(134) / 230.1 (96) 20–39 ..... 225.8(551) / 227.8(350) >40 ..... 229.0(114) / 238.5 (68) Pipe and cigar ..... 214.9(128) / 227.1(116)	The authors conclude that there is evidence of a gradient of cholesterol with increasing amount of cigarette smoking in younger men.
Karvonen et al., 1959, Finland (97).	525 males in various occupations 20–59 years of age.	*Serum cholesterol mg. percent* *West Finland* / *East Finland* / *Helsinki* NS ..... 205.0(64) 226.6 (39) 235.1 (62) SM ..... 228.7(91) 249.7(103) 257.8(166)	The authors state that no trend was noted associating increasing amount smoked with increasing serum cholesterol, although smokers and nonsmokers did have different overall means.

(72) GOFMAN, J. W., LINDGREN, F. T., STRISOWER, B., DELALLA, O., GLAZIER, F. TAMPLIN, A. Cigarette smoking, serum lipoproteins, and coronary heart disease. Geriatrics 10(8); 349–354, August 1955.

(185) THOMAS, C. B. Familial and epidemiologic aspects of coronary disease and hypertension. Journal of Chronic Diseases 7(3): 193–208, March 1958.

(47) DAWBER, T. R., KANNEL, W. B., REVOTSKIE, N., STOKES, J., KAGAN, A., GORDON, T. Some factors associated with the development of coronary heart disease. Six years' followup experience in the Framingham study. American Journal of Public Health and the Nation's Health 49(10): 1349–1356, October 1959.

(97) KARVONEN, M., ORMA, E., KEYS, A., FIDANZA, F. BROZEK, J. Cigarette smoking, serum-cholesterol, blood-pressure, and body fatness. Observations in Finland. Lancet 1: 492–494, March 7, 1959.

(1) ACHESON, R. M., JESSOP, W. J. E. Tobacco smoking and serum lipids in old men. British Medical Journal 2: 1108–1111, October 28, 1961.

(31) BRONTE-STEWART, B. Cigarette smoking and ischaemic heart disease. British Medical Journal 1: 379–384, February 11, 1961.

(119) KONTTINEN, A. Cigarette smoking and serum lipids in young men. British Medical Journal 1: 1115–1116, April 21, 1962.

(26) BLOMSTRAND, R., LUNDMAN, T. Serum lipids, smoking and heredity. Acta Medica Scandinavica 180(Supplement 455): 51–60, 1966.

1005050767

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

TABLE A7.—*Differences in serum lipids between smokers and nonsmokers (cont.)*

(Actual number of individuals shown in parentheses)[a]

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results	Comments
Higgins and Kjelsberg, 1967, U.S.A. (83).	5,030 male and female residents of Tecumseh, Michigan, 16–79 years of age.	*Males* / *Females* NS ..... 209.9 (360) / 210.1 (1,439) Cigarette ..... 212.5 (1,426) / 212.4 (910)	
Pincherly and Wright, 1967, England (150).	2,000 men participating in executive health examinations 28–70 years of age.	*Serum cholesterol mg. percent* / *Percentage with serum cholesterol >270 mg. percent* NS (677) ..... 236.2 / 19.0 Ex-smoker (388) ..... 246.0 / 28.0 1–19 cigarettes/day (424) ..... 239.2 / 24.0 >20 cigarettes/day (611) ..... 249.4 / 30.0	The authors noted that smokers showed significantly higher ($p<0.001$) serum cholesterol levels than nonsmokers.
Van Buchem, 1967, Netherlands (199).	918 randomly chosen males 40–59 years of age for entry into prospective study.	*Serum cholesterol* *0–209 mg. percent* / *210–249 mg. percent* / *>250 mg. percent* NS ..... 12.4 (32) / 14.0 (44) / 14.2 (41) Cigarette SM ..... 71.6 (184) / 67.8 (213) / 68.2 (197) Other ..... 16.0 (41) / 18.2 (57) / 17.6 (51)	The authors found no correlation between smoking and serum cholesterol levels.
Boyle et al., 1968, U.S.A. (28).	1,104 male factory employees 20–64 years of age.	*Serum cholesterol mg. percent* / *Serum Beta-lipoprotein mg. percent* NS ..... 243 (519) / 0.325 SM ..... 251 (576) / 0.352 $p<0.005$ / $p<0.001$	Beta-lipoproteins were found to increase with age, but smokers had higher levels than nonsmokers at all ages.
Caganova et al., 1968, Czechoslovakia (56).	49 males living in youth hostel, 21.6 average age.	*Serum cholesterol mg. percent* / *Serum Beta-lipoprotein mg. percent* NS(34) ..... 188.20 / 359.80 SM(15) ..... 214.20 / 458.40 $p<0.025$ / $p<0.001$ *Beta/alpha lipoprotein ratio* NS(34) ..... 1.10 SM(15) ..... 1.85 $p<0.025$	

(Actual number of individuals shown in parentheses)[a]

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results	Comments
Fidanza et al., 1966, Italy (62).	111 male prisoners 34–59 years of age.	*Serum cholesterol mg. percent* *Ages <19* / *20–29* / *30–39* / *40–49* NS .... / 195 (12) / 189 (10) / 176 (7) <20 cigarettes/day ..... 208 (5) / 201 (16) / 202 (13) / 155 (10) >20 cigarettes/day ..... 197 (6) / 175 (7) / 171 (7) / .. *Serum triglycerides mg. percent* NS .... / 84.7 / 71.9 / 85.0 <20 cigarettes/day ..... 84.5 / 89.4 / 101.9 / 89.8 >20 cigarettes/day ..... 81.0 / 86.0 / 65.7 / ..	No statistically significant differences found between SM and NS.
Kedra and Dmowski, 1966, Poland (99).	200 clinically healthy males 20–50 years of age.	*Serum cholesterol mg. percent* / *Phospholipids mg. percent* / *Total lipids mg. percent* NS(100) ..... 170.2 / 265.1 / 1,234.8 SM 100) ..... 224.9 / 257.5 / 1,362.1 $p<0.01$ / $p>0.05$ / $p<0.01$ *Total fatty acids mg. percent* / *Beta-lipoproteins percent of total lipoproteins* NS(100) ..... 797.8 / 43.1 SM 100) ..... 869.9 / 49.9 $p<0.01$ / $p<0.01$	Serum cholesterol also noted to increase with increasing intensity and duration of smoking.
Harlan et al., 1967, U.S.A. (79).	657 former naval aviation cadets 48 years of age (average).	*Serum cholesterol* Found to be related to cigarette smoking $p<0.05$.	*Serum triglycerides* Found not to be related to cigarette smoking.	*Lipoproteins* Sf 0–12 related. $p<0.05$ Sf 20–100 unrelated. Sf 100–400 unrelated.	
Heyden-Stucky and Schibler-Reich, 1967, Switzerland (82).	600 plant workers 30–60 years of age.	*Serum cholesterol mg. percent* / *Serum triglycerides mg. percent* <10 cigarettes/day ..... 210.0 (334) / 110.0 >10 cigarettes/day ..... 260.0 (166) / 180.0	No statistically significant difference found between SM and NS.

(62) FIDANZA, F., IMBIMBO, B., DI BENEDETTA, C. Indagine epidemiologica delle cardiopatie ischemiche nei reclusi del penitenziario di S. Stefano di Ventotene. (Epidemiological investigation of ischemic heart disease in prisoners of S. Stefano di Ventotene prison.) Giornale dell' Arteriosclerosi 4: 253–267, 1966.

(99) KEDRA, M., DMOWSKI, G. The influence of tobacco smoking on the development of atherosclerosis and on the composition of blood lipids. Polish Medical Journal 5(1): 37–43, 1966.

(79) HARLAN, W. R., OBERMAN, A., MITCHELL, R. E., GRAYBIEL, A. Constitutional and environmental factors related to serum lipid and lipoprotein levels. Annals of Internal Medicine 66(3): 540–555, March 1967.

(82) HEYDEN-STUCKY, S., SCHIBLER-REICH, S. Kardiologische Risikofaktoren bei Schweizer Mannern. (Cardiological risk factors in Swiss men.) Schweizerische Medizinische Wochenschrift 97(1): 20–25, January 7, 1967.

(83) HIGGINS, M. W., KJELSBERG, M. Characteristics of smokers and nonsmokers in Tecumseh, Michigan. II. The distribution of selected physical measurements and physiologic variables and the prevalence of certain diseases in smokers and nonsmokers. American Journal of Epidemiology 86(1): 60–77, July 1967.

(150) PINCHERLE, G., WRIGHT, H. B. Screening in the early diagnosis and prevention of cardiovascular disease. Journal of the College of General Practitioners 13: 280–289, 1967.

(199) VAN BUCHEM, F. S. P. Serum lipids, nutrition and atherosclerotic complications in man. Acta Medica Scandinavica 181(4): 403–416, April 1967.

(28) BOYLE, E., JR., MORALES, I. B., NICHAMAN, M. Z., TALBERT, C. R., JR., WATKINS, R. S. Serum beta lipoproteins and cholesterol in adult men. Relationships to smoking, age, and body weight. Geriatrics 23(12): 102–111, December 1968.

(56) CAGANOVA, A., CAGAN, S., SIMKO, V. Lipidy krvneho sera u nefajciarov a fajciarov. (Blood serum lipids in nonsmokers and smokers.) Bratislavske Lekarske Listy 50(3): 387–392, September 3, 1968.

1005050768

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

TABLE A7.—*Differences in serum lipids between smokers and nonsmokers (cont.)*

(Actual number of individuals shown in parentheses)[a]

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results			Comments
Modzielewski and Malec, 1969, Poland (*133*).	140 males 20–68 years of age.	*Serum cholesterol* NS (20) p<0.01 Heavy smokers	*Serum Beta-lipoproteins* NS p<0.01 Heavy smokers	*Serum free fatty acids* NS p<0.01 Heavy smokers	
Kjeldsen, 1969, Denmark (*115*).	934 employees of various firms in Copenhagen.	*Serum cholesterol mg. percent* NS (196) ..... 236 SM (735) ..... 241 } p<0.01			
Pozner and Billimoria, 1970, England (*151*).	64 male and female healthy volunteers 19–30 years of age.		*Serum cholesterol mg. percent*	*Serum triglycerides mg. percent*	*Total phospholipids mg. percent*	Significant figures refer to heavy smokers as compared with nonsmokers.
		NS (20)	176.3	68.6	193.4	
		Light SM (17) ..... (Over 7.3 cigarettes/day)	172.1	68.4	188.9	
		Heavy SM (27) ..... (Over 22.8 cigarettes/day)	200.0 p<0.05	67.6 p>0.05	216.6 p<0.001	

[a] Unless otherwise specified, disparities between the total number of cases and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

(*133*) MODZELEWSKI, A., MALEC, A. Zachowanie sie niektorych lipidow we krwi u palaczy. (Patterns of certain blood lipids in smokers.) Wiadomosci Lekarskie 22(3): 229–233, February 1, 1969.

(*151*) POZNER, H., BILLIMORIA, J. D. Effect of smoking on blood-clotting and lipid and lipoprotein levels. Lancet 1(7660): 1318–1321, June 20, 1970.

(*56*) EDWARDS, F., MCKEOWN, T., WHITFIELD, A. G. W. Association between smoking and disease in men over sixty. Lancet 1: 196–200, January 24, 1959.

(*43*) CLARK, V. A., CHAPMAN, J. M., COULSON, A. H. Effects of various factors on systolic and diastolic blood pressure in the Los Angeles Heart Study. Journal of Chronic Diseases 20: 571–581, 1967.

TABLE A8.—*Blood pressure differences between smokers and nonsmokers*

(Actual number of individuals shown in parentheses)[a]

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results				Comments
Dawber et al., 1959, U.S.A. (*47*).	1,253 male and female residents of Framingham.		*Systolic blood pressure*			No association found between systolic blood pressure and smoking.
			Ages 38–44	*45–59*	
		NS (149)	128.8	143.0	
		Cigarettes (574)	132.5	140.3	
		<10 (75)	124.7	144.0	
		10–19 (154)	129.4	141.6	
		20–39 (551)	132.2	138.9	
		>40 (114)	136.1	141.5	
		Pipe and cigar (128)	135.0	141.9	
Edwards et al., 1959, England (*56*).	1,737 male patients of general practitioners over 60 years of age.	*Proportion of males with "Hypertension" (≥200/≥100 mm. Hg.)*				
		NS ..... 27.2 percent (151)				
		Cigarettes ..... 20.5 percent (720)				
		Pipe ..... 25.9 percent (341)				
Karvonen et al., 1959, Finland (*87*).	525 males in various regions of Finland 20–69 years of age.		*Systolic blood pressure*			No data on pipe and cigar smokers. No statistical significance noted.
			West Finland	*East Finland*	*Helsinki*	
		NS	139.2 (64)	142.6 (39)	132.8 (62)	
		SM	138.3 (91)	135.4 (103)	129.8 (166)	
			Diastolic blood pressure			
		NS	84.7	86.8	89.6	
		SM	81.9	84.1	86.8	
Clark et al., 1967, U.S.A. (*43*).	1,859 male civil servants.		*Mean systolic blood-pressure*		*Mean diastolic blood-pressure*	Nonsmoker and smoker groups were of similar average age.
		NS (728)	137.0 } (p≤0.05)		83.9 } (p≤0.05)	
		SM (607)	133.6		82.6	

1005050769

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

Serum Lipid Differences. The tabulated material of (151) Pozner and Billimoria was subsequently challenged by Howell in a letter to the Editor (Br Med J 22 April 1972).

Smoking and Vascular Disease

SIR,—Your leading article (1 April, p. 3) states unequivocally, "The medical profession is the only professional group in which cigarette smoking has lessened," without the support of any references. I would doubt if each and every professional group has been adequately sampled and reported on. *Smoking and Health Now*[1] reports that after the publication of the 1962 report there was a sharp reduction in the number of men smoking cigarettes, a reduction maintained in social classes I, II, and III. The professional groups fall in these classes.

Your article goes on to point out that Pozner and Billimoria[2] (in a small selected sample) found that "fasting plasma turbidity, cholesterol, and β and pre-β lipoproteins were significantly increased in heavy smokers," but you failed to make the most important point that in male heavy smokers only pre-β lipoprotein means were significantly higher than those of non-smokers. In a sample of 2,433 middle-aged males Howell[3] failed to find significant correlation between smoking and haemoglobin, E.S.R., serum cholesterol, β lipoprotein, and uric acid levels. The one striking finding—namely, a significantly increased white blood cell count in heavy smokers—has now been confirmed by Corre, Lellouch, and Schwartz.[4] In some small way this may provide confirmation that the sample used by Howell was not atypical for males of that age group with an average smoking history extending over 20 years.—I am, etc.,

R. W. HOWELL

Tilehurst, Berks

1 Royal College of Physicians, *Smoking and Health Now*. London, Pitman, 1971.
2 Pozner, H., and Billimoria, J. D., *Lancet*, 1970, 1, 1313.
3 Howell, R. W., *Lancet*, 1970, 2, 152.
4 Corre, F., Lellouch, J., and Schwartz, D., *Lancet*, 1971, 2, 632.

100505070

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

Hypertension in Nonsmokers. The articles which do not show the health hazards of smoking are inserted in these tables. This is unfortunate, because the significance of the observations are lost and buried underneath the selected papers. The Results of (56) Edwards are as follows:

Hypertension

In view of the continuous distribution of arterial pressure, a full assessment of the effect of smoking requires a more critical appraisal than we can attempt here. Nevertheless the limited data available for the preliminary note suggested that, even when men are identified arbitrarily as hypertensive (that is with systolic or diastolic pressures above 200 or 100 mm. Hg respectively), a relationship to smoking was apparent. It was therefore thought worth while to use the data now available for all men over 60 for a more complete examination of this relationship.

TABLE XI—PROPORTION (%) OF MEN WITH HYPERTENSION ACCORDING TO SMOKING HABITS AND AGE

Age (yr.)	Men not smoking	Men smoking		All men who have never smoked cigarettes
		Cigarettes	Pipe	
60–64	14·9	14·9	13·9	16·3
65–69	21·4	12·2	17·6	20·2
70–74	40·4	34·7	31·3	35·5
75 and over	36·5	32·0	34·7	35·1
Total	24·2	20·5	25·9	27·2

TABLE XII—PROPORTION (%) OF MEN WITH HYPERTENSION ACCORDING TO SMOKING HABITS AND SOCIAL CLASS

Social class	Men not smoking	Men smoking		All men who have never smoked cigarettes
		Cigarettes	Pipe	
I & II	24·5	18·9	20·3	21·6
III	31·1	19·8	28·0	30·2
IV & V	24·1	23·1	26·1	24·8

Table XI gives the percentages of men with pressures above the limits referred to according to age and smoking habits. As would be expected, the percentages are much higher above than below 70, although they do not appear to differ appreciably in the age-groups 70–74 and 75 and over. But at all ages the incidence of hypertension is lower in cigarette-smokers than in men not smoking. The frequency in pipe-smokers is intermediate between that of the two previous groups, but is much nearer to the level in cigarette-smokers than in men not smoking. In this case, therefore, unlike the two previously considered, the effect on arterial pressure seems to be common to cigarette- and pipe-smokers.

The relationship between the incidence of hypertension and social class (table XII) is not regular. High pressures are, however, less common in cigarette-smokers than in men not smoking.

Discussion

Some of the criticisms of the evidence relating smoking to disease are overcome by investigation of a random sample of the general population. By this method it is possible to examine the frequency of disease in smokers and non-smokers—a procedure less open to criticism than a comparison of the smoking habits of the affected individuals with those of a control group. Already some fairly large populations have been assembled in which the incidence of mortality from specific diseases has been related to smoking. But data in respect of morbidity are also required, and the populations which can be studied are inevitably much smaller. In practice investigation of the effects of smoking on morbidity in a sample of the general population is almost inevitably restricted to the common diseases.

In the present assessment of the effects of smoking in 1737 representative men over the age of 60, we have considered only the eight most common diseases or disabilities. Three diseases—bronchitis, peptic ulcer, and hypertension—were consistently related to smoking habits. Bronchitis and peptic ulcer were commoner in men smoking than in men not smoking and increased in frequency with increasing amounts smoked. The incidence of both diseases was higher in poorly paid (classes IV and V) than in well-paid occupations (classes I and II). The relationship of smoking to incidence, however, appeared to be independent of social class. (Expressed differently, in all classes the frequency of the diseases was increased by smoking.) In general the experience of pipe-smokers was about the same as that of men not smoking, the increased risks being apparently restricted to cigarette-smokers. The observations on bronchitis are consistent with previous reports (Oswald and Medvei 1955, Ogilvie and Newell 1957), and those on peptic ulcer confirm and extend results described by Doll et al. (1958).

The frequency of hypertension (arterial pressures above 200 mm. Hg systolic or 100 mm. Hg diastolic) was greater in men not smoking than in cigarette- or pipe-smokers, and in this case incidence was inversely related to amounts smoked. This finding was observed in each of the occupational groups considered, but there was no consistent relationship between incidence and social class. Pressures in men who had given up smoking were approximately the same as in those who had never smoked. These results suggest that the lowering of arterial pressure produced by smoking is a short-term one and disappears after smoking is stopped for a period.

For reasons referred to earlier, in interpretation of the effects of smoking the common conditions whose incidence was not associated with it—coronary-artery disease, arthritis, defective hearing, and defective vision—are almost as significant as those which are. It must be remembered, of course, that observations on living men are incomplete; for example, there is a good deal of evidence that mortality due to coronary-artery disease is related to smoking (Hammond and Horn 1954, Doll and Hill 1956). Nevertheless the facts that the common diseases with which smoking is so consistently associated are those in which an oral or respiratory irritant might be expected to be significant, and in which smoking had been mentioned as an aetiological influence long before there was direct evidence, meet to some extent the reservation that smokers as a class may be genetically more susceptible to the diseases associated with smoking.

1005050721

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

TABLE A3.—*Blood pressure differences between smokers and nonsmokers (cont.)*

(Actual number of individuals shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results					Comments
Higgins and Kjelsburg, 1967, U.S.A. (83).	5,030 male and female residents of Tecumseh, Michigan, 16–79 years of age.		*Age adjusted mean systolic blood pressure*		*Age adjusted mean diastolic blood pressure*		
			Males	*Females*	*Males*	*Females*	
		NS	127.9 (360)	84.5 (1419)	136.6 (360)	82.1 (1420)	(p<0.001)
		Cigarette	136.4 (1426)	81.4 (910)	131.8 (1426)	79.0 (910)	
Reid et al., 1967, England (155).	676 male British and 625 male American postal workers 40–59 years of age.		*Mean systolic blood pressure (adjusted for difference in weight)*		*Mean diastolic blood pressure*		The author did note SM-NS blood pressure differences prior to controlling for weight, but not after such control.
			UK	*U.S.A.*	*UK*	*U.S.A.*	
		NS	128.2 (45)	126.8 (99)	78.5	81.0	
		1–14 grams	130.2 (27)	133.0 (60)	79.4	82.1	
		15–24 grams	128.5 (232)	127.7 (169)	78.6	77.8	
		>25 grams	127.9 (70)	128.1 (218)	77.5	77.1	
		All amounts	129.1 (519)	128.6 (417)	78.7	77.8	
Tibblin, 1967, Sweden (157).	895 males in Göteborg, Sweden, born in 1913.		*Blood pressure* ≤110/≤70 (88)	*115–115/ 75–95 (463)*	*130–170/ 100–110 (220)*	>175/>115 (78)	Numbers in parentheses represent total in blood pressure group. The author noted a stepwise decrease with level of blood pressure as smoking increased.
		NS	18.0	25.0	25.5	34.7	
		1–14 cigarettes	29.2	29.2	25.5	18.7	
		>15 cigarettes	28.1	30.9	18.5	17.3	
		Pipe and cigar	11.2	5.6	10.0	4.0	

[1] Unless otherwise specified, disparities between the total number of individuals and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

(157) TIBBLIN, G. High blood pressure in men aged 50. A population study of men born in 1913. Acta Medica Scandinavica (Supplementum 470): 1–84, 1967.

TABLE A17.—*Incidence of new coronary heart disease by smoking category and behavior type for men 39–49 years of age*

(Numbers in parentheses are number of CHD cases in each subgroup)

Behavior type	Smoking group						
	Never smoked	Former cigarette smokers	Current and former pipe and cigar only	Cigarettes			Total
				1–15	16–25	26 and over	
A	16.3 (5)	13.8 (7)	1.3 (1)	1.6 (1)	15.8 (16)	14.9 (16)	9.3 (46)
B	1.3 (2)	5.1 (3)	2.2 (2)	7.3 (4)	3.1 (3)	4.9 (4)	3.3 (18)
Total	2.9 (7)	9.1 (10)	1.8 (3)	4.9 (5)	9.3 (13)	10.4 (20)	6.2 (63)

Source	Analysis of variance table				
	Sum of squares	d.f.	Mean square	F	P
Within cells	59.471	2,245	0.026	..	..
Regression on age	0.458	1	0.458	17.296	0.001
Between smoking groups[2]	0.504	5	0.101	3.81	0.002
Between behavior types[2]	0.329	1	0.329	12.43	0.001
Interaction	0.396	5	0.079	2.99	0.011

[1] Rates are age-adjusted annual incidence per 1,000 men.

[2] Mean squares for "between smoking groups" and "between behavior types" are each computed eliminating the general mean and the other main effect but ignoring interaction, thus yielding an estimate of each main effect unconfounded by other significant main effects.

Source: Jenkins, C. D. et al. (90).

10050722

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

TABLE A18.—*Incidence of new coronary heart disease by smoking category and behavior type for men 50–59 years of age*

(Numbers in parentheses are number of CHD cases in each subgroup)

Behavior type	Never smoked	Former cigarette smokers	Current and former pipe and cigar only	Smoking group: Cigarettes 1–15	Cigarettes 16–25	Cigarettes 26 and over	Total
A	[1]12.4(5)	18.6(8)	21.8 (8)	16.4(5)	21.6 (9)	30.0(14)	20.4(49)
B	10.0(4)	5.1(1)	8.4 (3)	4.7(1)	21.1 (7)	10.1 (6)	12.0(21)
Total	11.1(9)	14.2(9)	14.9(11)	11.5(6)	21.3(16)	26.0(19)	16.8(70)

Source	Analysis of variance table: Sum of squares	d.f.	Mean square	F	P
Within cells	63.527	911	0.070	..	..
Regression on age	0.177	1	0.177	2.54	0.111
Between smoking groups[2]	0.522	6	0.104	1.496	0.188
Between behavior types[2]	0.296	1	0.296	4.24	0.040
Interaction	0.129	6	0.026	0.37	0.870

[1] Rates are age-adjusted annual incidence per 1,000 men.

[2] Mean squares for "between smoking groups" and "between behavior types" are each computed eliminating the general mean and the other main effect but ignoring interaction, thus yielding an estimate of each main effect unconfounded by other significant main effects.

SOURCE: Jenkins, C. D. et al. (*90*).

TABLE A20.—*Experiments concerning the effects of smoking and nicotine on animal cardiovascular function*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Cardiac output	Coronary blood flow	Comments
Bellet et al., 1941, U.S.A. (*81*).	39 experiments on dogs which had undergone coronary artery ligation up to 45 days before.	Inhalation of tobacco smoke in chamber.	Definite increase.	Definite increase.			Coronary artery ligation increased the frequency of nicotine-induced severe arrhythmias; these became less evident with increasing time since ligation.
		Nicotine intravenous 0.2-1.2 mg./kg.	Definite increase.	Definite increase.			
Burn and Rand, 1958, England (*85*).	10 rabbits, 5 experimental, 5 control; isolated atria.	Experimental animals pretreated with intraperitoneal nicotine and the atria of both groups excised and perfused with nicotine.					Isolated atrial specimen showed increased rate and increased amplitude of contractions with administration of nicotine proportional to pretreatment. These reactions were blocked by reserpine, and the authors consider nicotine effects to be mediated by catecholamine release from chromaffin store in myocardium.
West et al., 1958, U.S.A. (*208*).	33 normal adult mongrel dogs.	Coronary intra-arterial nicotine: I. 0.2-2.2 μg./kg. II. 0.04-1 μg./kg.	Definite increase (systolic).				I. Myocardial contractility increased 40–90 percent in 15/16 animals tested accompanied by ST segment depression and T-wave inversion and blocked by tetraethylammonium chloride. II. Coronary blood flow increased 19 percent upon left circumflex artery injection; coronary blood flow showed no change upon left anterior descending artery injection, 64 observations on 10 dogs. (Tetraethylammonium chloride blocked CBF increase.) The authors found no evidence of coronary vasoconstriction in these healthy animals.

1005050723

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

TABLE A20.—*Experiments concerning the effects of smoking and nicotine on animal cardiovascular function (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Cardiac output	Coronary blood flow	Comments
Forte et al., 1960, U.S.A. (65).	27 observations on 8 dogs.	Intravenous nicotine up to 21.5 mg. given as 5–15 μg./kg./minute.		Definite initial increase then decrease.		No change.	No significant change in either left ventricular work or myocardial oxygen extraction.
Kien and Sherrod, 1960, U.S.A. (111).	21 adult dogs	Cigarette smoke under positive pressure via tracheostomy. Nicotine 20 μg./kg. intravenously. Epinephrine 5 μg./kg. intravenously.		Definite increase.	Definite increase.	Increase following increase in blood pressure and cardiac output.	Effects of cigarette smoke were duplicated by intravenous nicotine and epinephrine. During cigarette smoke inhalation, it was noted that without blood pressure or output changes, coronary blood flow did not increase and that while adverse EKG changes were noted they correlated more closely with decreased cardiac oxygen utilization than with actual cardiac work.
Travell et al., 1960, U.S.A. (189).	14 normal rabbits and 18 rabbits with severe cholesterol-induced atherosclerosis.	Intravenous nicotine 0.01–0.1 mg.				Definite increase in normals.	Nicotine-induced coronary blood flow and heart rate increase in the atherosclerotic animals required 10 times and 2 times, respectively, the amounts required in the normal animals.

(65) FORTE, I. E. WILLIAMS, A. J. POTGIETER, L., SCHMITTHENNER, J. E., HAFKENSCHIEL, J. H., RIEGEL, C. Coronary blood flow and cardiac oxygen metabolism during nicotine-induced increases in left ventricular work. Annals of the New York Academy of Sciences 90(1): 174–185, September 27, 1960.

(124) LARSON, R. K., FUKUDA, P., MURRAY, J. F. Systemic and pulmonary vascular effects of nicotine in anesthetized dogs. American Review of Respiratory Diseases 91(4): 556–564. April 1965.

TABLE A20.—*Experiments concerning the effects of smoking and nicotine on animal cardiovascular function (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Cardiac output	Coronary blood flow	Comments
Bellet et al., 1962, U.S.A. (22).	I. 10 normal dogs II. 9 dogs at varying intervals following coronary artery ligation. III. 7 dogs with varying grades of artificially-induced coronary artery narrowing.	Intravenous nicotine, 20 μg./kg./minute for 15–20 minutes.				I. 125 percent increase II. 82.6 percent increase III. 83.3 percent increase	The authors noted that: 1. The response of coronary blood flow to nicotine resembled that of anoxemia in the presence of coronary insufficiency. 2. The greater the induced coronary impairment the smaller the increment in coronary blood flow.
Leaders and Long, 1962, U.S.A. (115).	15 adult mongrel dogs.	Left anterior descending intracoronary injection of nicotine or norepinephrine.					Nicotine and norepinephrine both increased coronary vascular resistance and myocardial contractile force (the former measured by a constant-volume variable-pressure system). The action of nicotine was blocked by pretreatment with hexamethonium, pentolinium, reserpine, or guanethidine.
Larson et al., 1965, U.S.A. (124).	13 adult mongrel dogs.	Intravenous nicotine, 0.02 mg./kg./minute for 10–12 minutes.		Definite increase.	Definite increase.		Systemic vascular resistance and pulmonary artery and left atrial pressures showed biphasic responses of increase followed by decrease.

1005050744

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

TABLE A20.—*Experiments concerning the effects of smoking and nicotine on animal cardiovascular function (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Comments
Folle et al., 1966, U.S.A. (64).	7 dogs of 33 investigated (Remainder experienced catheterization failures).	I. Cigarette smoke inhalation to isolated left lower lobe and then blood perfused coronary arteries. II. Cigarette smoke to rest of lung and then blood passed to general circulation. III. Nicotine perfused directly into left coronary artery.	I. No change in coronary vascular resistance. II. 5/6 showed increase in coronary vascular resistance due, according to the author, to general sympathetic nervous system stimulation. III. 4/6 showed increase in coronary vascular resistance. The authors conclude that the cardiac effects of tobacco arise almost entirely from the extracardiac actions of smoking instead of the direct response of the heart.
Nadeau and James, 1967, U.S.A. (148).	26 dogs	Nicotine 0.01–10.0 μg. into sinus node artery.	Heart rate showed initial slowing (due probably to vagal stimulation) followed by acceleration (due probably to vagal paralysis and catecholamine release). No systemic blood pressure changes noted.
Romero and Talesnik, 1967, U.S.A. (156).	16 experiments on isolated cat heart.	Nicotine in varying doses in perfusate of coronary arteries.	Over 5 μg. of nicotine was found to produce an initial bradycardia associated with increased coronary flow, followed by prolonged tachycardia with an initial decrease in coronary blood flow followed by a prolonged increase. Pretreatment with hexamethonium or reserpine prevented both the myocardial stimulation and the increase in coronary blood flow. The authors consider the action of nicotine to be a combination of a direct vasoconstrictive effect and an indirect catecholamine-releasing vasodilating effect.
Puri et al., 1968, U.S.A. (153).	12 mongrel dogs	I. (14) Intravenous nicotine 50 μg./kg./minute for 3–4 minutes II. (8) Propranolol pretreatment, then 50 μg./kg./minute nicotine for 3–4 minutes	I. Nicotine produced a definite increase in the force and velocity of left ventricular contraction. II. Pretreatment with propranolol produced (relative to results of Group I): (a) A further increase in left ventricular systolic pressure. (b) A decrease in velocity of shortening. (c) A significant increase in left ventricular end-diastolic pressure. The authors conclude that propranolol probably impairs the norepinephrine-like effects of nicotine on the myocardium while enhancing its peripheral vasopressor effects.

(64) FOLLE, L. E., SAMANEK, M., AVIADO, D. M. Cardiopulmonary effects of tobacco and related substances. II. Coronary vascular effects of cigarette smoke and nicotine. Archives of Environmental Health 12(6): 712–715. June 1966.

(152) PURI, P. S., ALAMY, D., BING, R. J. Effect of nicotine on contractility of the intact heart. Journal of Clinical Pharmacology 8(5): 295–301, September–October 1968.

TABLE A20.—*Experiments concerning the effects of smoking and nicotine on animal cardiovascular function (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Comments
Balazs et al., 1969, U.S.A. (16).	Beagle dogs with lesions induced in myocardium by either: (1) Isoproterenol pretreatment, or (2) ligation of the anterior descending coronary artery.	I. Normals (3–6 per experiment): (a) 4 μg./kg. intravenous nicotine, (b) 40 μg./kg. intravenous nicotine. II. Experimental (3): 4 μg./kg. intravenous nicotine	I. (a) No evidence of arrhythmias; (b) A single or a few ectopic beats in 2/3 normal dogs. II. Extrasystoles noted in 2/3 animals during the first day after cessation of the arrhythmia induced by the lesion alone, but not thereafter. These and nicotine-induced arrhythmias were of a short duration.
Greenspan et al., 1969, U.S.A. (74).	Cardiac muscle isolated from the right ventricle of 10 adult dogs.	Nicotine 2–100 μg./cc. in Tyrode's solution perfusate.	Nicotine perfusion produced: (1) An increase in myocardial contractile force apparently independent of adrenergic innervation. (2) An increased automaticity of the Purkinje fiber system apparently due to release of catecholamines from chromaffin tissue stores. (3) A decrease in conduction velocity. The authors conclude that the latter two effects probably predispose to arrhythmia formation.
Saphir and Rapaport, 1969, U.S.A. (166).	88 mongrel cats	Nicotine 5–12 μg./kg. injected intraarterially to mesenteric circulation.	I. Mesenteric injection of nicotine was followed with 1–2 seconds by: (a) Increased left ventricular systolic pressure (LVSP). (b) Increased systemic resistance. (c) Enhanced myocardial performance. II. Left ventricular injection of nicotine was followed by: (a) Increased LVSP. (b) Bradycardia. (c) Enhanced myocardial performance greater than that seen in mesenteric-injected group. III. Pretreatment with phenoxybenzamine diminished the increase in LVSP while propranolol pretreatment diminished the enhancement of myocardial performance while LVSP still showed a significant increase. IV. Mesenteric sympathetic nerve section led to a diminished response. The authors conclude that the cardiovascular responses to nicotine may be neurogenic in nature with receptors distributed in certain abdominal arteries.

1005050775

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

TABLE A20.—*Experiments concerning the effects of smoking and nicotine on animal cardiovascular function (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Comments
Leb et al., 1970, U.S.A. (*158*).	12 mongrel dogs and CBF measured with use of Rb^{86} and digital counter.	Nicotine 100 μg./kg. for 2 minute intravenously.	Effective Coronary Flow (ECF) is that part of the total coronary flow (TCF) which is "effectively" involved in nutrient exchange. Nicotine injection was followed by: (1) 95.6 percent increase in TCF. (2) 61.1 percent increase in ECF. (3) 73.1 percent increase in myocardial oxygen consumption and analysis revealed that capillary flow increased almost proportionately to myocardial oxygen consumption whereas the increase in TCF was far in excess. (4) Definite increases in cardiac output, heart rate, left ventricular work, and aortic pressure.
Ross and Biess, 1970, U.S.A. (*169*).	10 dogs undergoing instantaneous coronary arterial flow measurement.	Nicotine 10–100 μg. intracoronary injection.	Nicotine injection was followed by: (1) Increased contractile force. (2) Decreased myocardial contraction time. (3) Decreased time necessary to reach peak tension. (4) Decreased total stroke systolic CBF. (5) Increased total stroke diastolic CBF. (6) Increased total stroke CBF. (7) Changes similar to intraarterial epinephrine. (8) Changes blocked by pentolinium pretreatment. (9) No change in heart rate or blood pressure. The authors conclude that catecholamines released from the ventricular myocardium mediated these responses to nicotine.

TABLE A21.—*Experiments concerning the effects of smoking and nicotine on the cardiovascular system of humans*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Russek et al., 1955, U.S.A. (*164*).	I. 23 healthy male smokers 21–40 years of age (average 42). II. 37 male patients with overt clinical CHD 42–70 years of age (average 54), 6 were nonsmokers.	1 standard and 1 denicotinized cigarette.	I. Increase. II. Increase.	Increase. Increase.	EKG: I. 16/23 showed significant changes. II. No significant changes. BCG: I. ... II. 18/37 showed significant change.				Denicotinized cigarettes evoked changes of a lesser degree in normals and CHD subjects, but in the latter group there was no significant difference between these changes.
Bargeron et al., 1957, U.S.A. (*17*).	16 of 30 healthy adult male volunteer smokers and nonsmokers who underwent successful catheterization 18–63 years of age.	1 cigarette inhaled at intervals of 20 seconds.	Insignificant increase.	Increase.				Definite increase.	Coronary vascular resistance fell significantly. Myocardial O_2 usage underwent no significant change. Pyruvate extraction fell slightly. Authors consider lack of increase in heart rate as due to baseline apprehensive tachycardia.

1005050276

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

TABLE A21.—*Experiments concerning the effects of smoking and nicotine on the cardiovascular system of humans (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Regan et al., 1960, U.S.A. (151).	7 males with history of EKG-proven myocardial infarction undergoing cardiac catheterization.	2 standard cigarettes in 25 minutes inhaled at minute intervals.	Definite increase.	Definite increase.			Increase.	No significant change.	Myocardial O_2 consumption rose slightly in 3 out of 7. The author considers that the EKG changes noted on smoking are probably due less to decreased coronary blood flow than to increased workload (oxygen need) where oxygen supply does not increase. Noted no evidence of myocardial ischemia during smoking.
Thomas and Murphy, 1960, U.S.A. (186).	113 clinically healthy young males.	One standard cigarette smoked at own pace.	Definite increase.	Definite increase.		Definite increase.	Definite increase.		Pulse pressure showed a decrease. Smokers responded slightly but significantly more actively than non-smokers. ECG changes were increasingly common with increasing age, weight, and serum cholesterol.

(186) THOMAS, C. B., MURPHY, E. A. Circulatory responses to smoking in healthy young men. Annals of the New York Academy of Sciences 90(1): 266–276, September 27, 1960.

TABLE A21.—*Experiments concerning the effects of smoking and nicotine on the cardiovascular system of humans (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Von Ahn, 1960, Sweden (201).	The author reviews a series of experiments performed between 1944–1956.	Cigarette smoking.	Increase.		EKG: Slight ST segment depression and T-wave flattening.				EKG changes more prominent in young, clinically healthy subjects than in older, habitual smokers. Intravenous nicotine and smoking showed identical cardiovascular effects. Smoking elicited angina pectoris in a number of CHD patients.
Irving and Yamamoto, 1962, England (89).	6 normal males, 15 patients with diseases not defined, 19–66 years of age, all moderate-heavy cigarette smokers.	(a) Sham smoking.	(a) No change.	No change.		(a) No change.	No change.		Cardiac output measured by dye dilution technique.
		(b) Non-inhalation smoking.	(b) No change.	No change.		(b) No change.	No change.		
		(c) 2 standard cigarettes in 10 minutes.	(c) Definite increase.	Widened pulse pressure.		(c) Definite increase.	Definite increase.		
		(d) Nicotine 0.6 mg. intravenously.	(d) Definite increase.	Definite increase.		(d) Definite increase.	Definite change.		

1005050777

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

TABLE A21.—*Experiments concerning the effects of smoking and nicotine on the cardiovascular system of humans (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Pentecost and Shillingford, 1954, U.S.A. (119).	I. 14 volunteers with clinical CHD, 13/14 smokers, average age 39.5.	Single cigarette smoked at own rate in 6–7 minutes.	Definite increase in all groups.	Definite increase in all groups.		I. 10 percent increase.	37 percent increase.		
	II. 6 patients with angina pectoris, all smokers, average age 43.4.					II. Intermediate change.	Intermediate change.		
	III. 14 patients with history of definite myocardial infarction, all smokers average age 54.1.					III. 8 percent decrease.	1 percent increase.		
Frankl et al., 1965, U.S.A. (67).	6 male and 3 female patients with healed myocardial infarction 48–69 years of age 2/8 nonsmokers.	2 standard cigarettes in 10 minutes at rest and under graded exercise.	Definite increase at rest and at exercise.			No significant changes at rest or during exercise.	No significant changes at rest or during exercise.		The author contrasts this response with that seen among healthy young individuals.

(171) SEN GUPTA, A. N., GHOSH, B. P. Observations on some cardiovascular and biochemical effects of tobacco smoking in health and in ischaemic cardiacs. Bulletin of the Institute of Post-Graduate Medical Education and Research 9(2): 45–57, April 1967.

TABLE A21.—*Experiments concerning the effects of smoking and nicotine on the cardiovascular system of humans (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Sen Gupta and Ghosh, 1967, India (171).	6 healthy male nonsmokers.	1 untipped cigarette in 5–7 minutes.	Increase in all groups.	Increase in all groups.	No change.				
	8 healthy male smokers.				6/8 showed ST changes.				
	6 patients with CHD, nonsmokers.				All showed ST and T-wave changes.				
	5 patients with CHD, smokers.				All showed ST and T-wave changes.				
	36–64 years of age.								
Aronow et al., 1968, U.S.A. (5).	10 male patients with classical angina pectoris. 32–59 years of age	1 standard high nicotine cigarette in 5 minutes.	Definite increase.	Definite increase.					Product of systolic blood pressure and heart rate showed a significant increase on smoking while left ventricular ejection time values did not. All patients developed angina more rapidly under a constant exercise load if they had smoked before exercising.
Kerrigan et al., 1968, U.S.A. (102).	24 male and 1 female healthy smokers, average age, 45.	2 filtered cigarettes in 15 minutes with measures taken at rest and during exercise.	Definite increase under rest and exercise conditions.	Definite increase under rest and exercise conditions.			Cardiac index. Definite increase under rest and exercise conditions.		The increase in cardiac index, heart rate, and blood pressure during exercise with smoking was the sum of such increases seen with smoking or exercise separately. Neither group showed increases in peripheral vascular resistance.
	8 male and 2 female healthy nonsmokers, average age 33.								

(5) ARONOW, W. S., KAPLAN, M. A., JACOB, D. Tobacco: A precipitating factor in angina pectoris. Annals of Internal Medicine 69(3): 529–536, September 1968.

(102) KERRIGAN, R., JAIN, A. C., DOYLE, J. T. The circulatory response to cigarette smoking at rest and after exercise. American Journal of the Medical Sciences 255(2): 113–119, February 1968.

1005050778

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

TABLE A21.—*Experiments concerning the effects of smoking and nicotine on the cardiovascular system of humans (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Allison and Roth, 1969, U.S.A. (5).	30 healthy male subjects. 32–59 years of age.	2 standard cigarettes smoked in 12–16 minute period.	Definite increase.	Increase.			Increase followed by decrease within 20 minutes.		Definite decrease in pulmonary blood volume as indicated by impedance methods of thoracic pulse volume.
Aronow and Swanson, 1969, U.S.A. (7).	10 male patients with classical angina pectoris. 32–59 years of age.	1 low nicotine cigarette in 5 minutes.	Definite increase.	Definite increase.					All patients developed angina sooner if they smoked before exercising.
Aronow and Swanson, 1969, U.S.A. (6).	10 male patients with classical angina pectoris. 32–59 years of age.	1 non-nicotine cigarette in 5 minutes.	No change.	No change.					No difference noted in time or onset of exercise-induced angina between smoking and non-smoking procedures.
Marshall et al., 1969, U.S.A. (129).	42 normotensive healthy male prisoners 18–50 years of age. 13 nonsmokers. 16 moderate smokers. 13 heavy smokers.	3/4 of one standard cigarette.	Insignificant increase.	Insignificant increase.					Blood pressure response to cold pressor test noted to be greater in heavy smokers. Presyncopal reactions to 40 degree head-up tilt more frequent in smokers.

(5) ALLISON, R. D., ROTH, G. M. Central and peripheral vascular effects during cigarette smoking. Archives of Environmental Health 19(2): 189–198, August 1969.

(7) ARONOW, W. S., SWANSON, A. J. The effect of low-nicotine cigarettes on angina pectoris. Annals of Internal Medicine 71(3): 599–601, September 1969.

(6) ARONOW, W. S., SWANSON, A. J. Non-nicotinized cigarettes and angina pectoris. Annals of Internal Medicine 70(6): 1227, June 1969.

(129) MARSHALL, W. J., JR., STANLEY, E. L., KEZDI, P. Cardiovascular effects of cold pressor tests, 40° head-up tilt, and smoking on smokers and nonsmokers. Diseases of the Chest 56(4): 290–296, October 1969.

TABLE A22.—*Experiments concerning the effect of nicotine or smoking on catecholamine levels*

Author, year, country, reference	Number and type of subject	Procedure	Results
Watts, 1960, U.S.A. (203).	11 dogs	0.02–0.60 mg/kg. nicotine intravenously.	Nicotine administration was associated with significant increases in peripheral arterial epinephrine levels. Ganglionic blocking agents prevented this effect.
Westfall and Watts, 1963, U.S.A. (210).	22 mongrel dogs	Cigarette smoking via tracheal cannula; 1 cigarette/8 minutes for 35 minutes.	Regular cigarette smoke evoked a statistically significant increase in adrenal vein, vena cava, and femoral artery levels of epinephrine. Cornsilk cigarette smoke evoked no change.
Westfall and Watts, 1964, U.S.A. (211).	21 male volunteers approximately 25 years of age; 11 nonsmokers, 10 smokers.	3 cigarettes smoked in 30 minutes.	Smoking at rate noted for 2½ hours evoked a significant increase in urinary epinephrine, but not norepinephrine levels.
Westfall et al., 1966, U.S.A. (208).	Mongrel dogs	Standard cigarette smoke exposure via endotracheal tube. Smoke inhalation every third inspiration for 8 minutes.	Smoke inhalation evoked a rise in cardiac output, stroke volume, blood pressure, and plasma catecholamine levels. Pretreatment with propranolol diminished the cardiac output and stroke volume responses but increased the blood pressure response—the latter effect due to the release of alpha-receptor activity by beta-blockade.

1005050779

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000

Author, year, country, reference	Number and type of animal	Procedure	Results
Adler et al., 1906, U.S.A. (*2*).	Rabbits	Nicotine 1.5 mg. intravenously in 6 percent solution 6 of 7 days per week for more than 4 months.	The authors noted an arteriionecrosis of the aorta, affecting mainly the inner muscular layers. Macroscopically, early changes consisted of small areas of calcareous ridging and aneurysmal dilatation without notable fatty degeneration or intimal discontinuity. Microscopically, early changes appeared in the muscle cells of the media, and "chalky" deposits were noted between the elastic fibers.
Hueper, 1943, U.S.A. (*86*).	I. 6 mongrel dogs.	Nicotine subcutaneously. Increasing dosage up up to 2.5 cc. of 3 percent solution for 1 month.	I. 4/6 animals died of infection and showed marked edema and focal hyalinization of the media of the aorta and large elastic arteries. 2/6 animals were sacrificed and showed thickening and hyalinization of the walls of the coronary arteries and edema of the media as well as endothelial proliferation of other arteries.
	II. 40 rats.	Increasing doses up to 1 cc. of 1 percent solution for 1 month.	II. Much less aortic involvement than that found in the dogs; infrequent arteriolar changes consisting of fibrosis and thickening of the media.
Maslova, 1956, USSR (*130*).	Rabbits	I. (10) Nicotine subcutaneously 1 percent solution 0.2 cc. daily for 115 days. II. (14) Nicotine plus 0.2 grams cholesterol per day. III. (10) Cholesterol only.	I. Aortic wall—acute swelling of elastic fibers with focal fragmentation and partial disintegration—no intimal fat deposits seen. Coronary vessels—thickening of the vessel wall—no fat deposits. II. Aorta—"massive" deposits of "cholesterol" in the intima and vasa vasorum with "loosening" of the aortic wall. Coronary vessels—the larger vessels showed moderate fat deposition and the smaller vessels showed swelling of the elastica. III. Aorta—isolated lipid deposition in the arch and ascending portions only. Coronary vessels—no fat deposition.
Czochra-Lyszewicz et al., 1959, U.S.A. (*46*).	Rabbits	I. (10) 1.0 g. cholesterol/day for 100 days. II. (10) Cholesterol plus 0.0015 g. nicotine/day intravenously. III. (4) Nicotine only.	Index of aortic lesion density (cholesterol infiltration): I. 2.6. II. 3.6. III. No aortic lesions noted.

(*2*) ADLER, I., HENSEL, O. Intravenous injections of nicotine and their effects upon the aorta of rabbits. Journal of Medical Research 15: 229–239, 1906.

(*86*) HUEPER, W. C. Experimental studies in cardiovascular pathology. VII. Chronic nicotine poisoning in rats and in dogs. A.M.A. Archives of Pathology 35: 846–856, 1943.

(*184*) THIENES, C. H. Chronic nicotine poisoning. Annals of the New York Academy of Sciences 90(1): 239–248, September 27, 1960.

TABLE A23.—*Experiments concerning the atherogenic effect of nicotine administration (cont.)*

Author, year, country, reference	Number and type of animal	Procedure	Results
Wenzel et al., 1959, U.S.A. (*187*).	Rabbits	I. (12) Control untreated. II. (12) Control diet plus 1 percent cholesterol and 5 percent cottonseed oil added. III. (12) Control diet plus oral nicotine 2.28 mg./kg./day. IV. (12) Regimen II plus oral nicotine 2.28 mg./kg./day. V. (12) Regimen II plus oral nicotine 1.42 mg./kg./day. VI. (12) Regimen II plus oral nicotine 0.57 mg./kg./day.	General findings: Marked aortic pathologic involvement was noted in all cholesterol-treated groups; however, no difference was noted between Group II. and Groups IV., V., and VI. Cardiac histopathology: I. No change. II. Advanced atherosclerotic changes in the subendocardial vessels. III. Thickening and fibrosis of coronary artery small branches. IV.–VI. More severe changes with greater fatty metamorphosis and actual early myocardial necrosis, but no dose-dependent effects observed.
Thienes 1960, U.S.A. (*184*).	Newborn rats and mice.	Nicotine subcutaneously up to 5 mg./kg. twice daily by the end of 1 month. Animals autopsied at 1 year.	No arterial pathology noted. Medial degeneration seen more frequently in controls. Suggests that older animals be used.
Grosgogeat et al., 1965, France (*75*).	Male rabbits	I. (10) Nicotine subcutaneously 0.75 mg./day. (10) Controls—saline injected. Sacrificed at from 20–120 days. II. (27) Same as Group I. (27) Controls—saline injected. Sacrificed at 90 days. III. (66) Nicotine subcutaneously 0.3–1.5 mg./day. Sacrificed at 30 days. IV. (24) Nicotine subcutaneously 0.75 mg./day. (24) Controls—saline injected. One-half of each group ate cholesterol-enriched diet (0.5–1.0 percent cholesterol added). Sacrificed at 60 days.	Significant differences in aortic subendothelial fibrosis between control and experimental groups noted only in II and IV. In group IV, the nicotine-treated group showed more severe changes.

1005050780

Source: https://www.industrydocuments.ucsf.edu/docs/kzlk0000